Accepted manuscript

A synthesis of pathways linking diet, metabolic risk and cardiovascular disease: a framework to guide further research and approaches to evidence-based practice

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This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI.
10.1017/S0954422421000378
Nutrition Research Reviews is published by Cambridge University Press on behalf of The Nutrition Society

Abstract

Cardiovascular disease (CVD) is the most common non-communicable disease occurring globally. Although previous literature have provided useful insights on the important role that diet play in CVD prevention and treatment, understanding the causal role of diets is a difficult task considering inherent and introduced weaknesses of observational (e.g., not properly addressing confounders and mediators) and experimental research designs (e.g., not appropriate or well-designed). In this narrative review, we organised current evidence linking diet, as well as conventional and emerging physiological risk factors with CVD risk, incidence and mortality in a series of diagrams. The diagrams presented can aid causal inference studies as they provide a visual representation of the types of studies underlying the associations between potential risk markers/factors for CVD. This may facilitate the selection of variables to be considered and the creation of analytical models. Evidence depicted in the diagrams was systematically collected from studies included in the British Nutrition Task Force report on Diet and CVD and database searches, including Medline and Embase. Although several markers and disorders linked to conventional and emerging risk factors for CVD were identified, the causal link between many remains unknown. There is a need to address the multifactorial nature of CVD and the complex interplay between conventional and emerging risk factors with natural and built environments, while bringing the life course and the role of additional environmental factors into the spotlight.

Keywords: Review, Cardiovascular disease, Risk factors, Diet, Nutritional status, Causality.

Introduction

Cardiovascular disease (CVD) is the most common non-communicable disease occurring globally and is responsible for about 18.6 million deaths every year [(1)], significantly impacting individuals who are in the peak productive period of life; consequentially placing an economic burden of billions of dollars on health care systems and the wider society [(2)]. Reducing premature mortality by a third from non-communicable diseases, including CVD, is a global priority put forth as part of the UN Sustainable Development Goals [(3)]. Better identification and management of CVD related risk factors could prevent thousands of premature deaths that result from CVD [(4)].

Diet is one factor that plays an important role in CVD prevention and treatment. Understanding the causal role of diets in the prevention and treatment of CVD would traditionally require randomized controlled trials (RCTs), as they are often considered the gold standard in establishing causal relationships. However, RCTs are not always the most appropriate or feasible design in nutrition research, particularly in the CVD area. For instance, RCTs can be costly as it can take several years before CVD outcomes can be directly measured. Observational prospective studies, which are the second option in terms of causality, are not without limitations. They are often criticized as unmeasured factors that influence both exposures and outcomes might be responsible for the relationship reported in studies. In addition, controlling for variables that mediate the relationship between exposures and outcomes can introduce errors in the estimation of effects [(5)]. Causal diagrams used in causal inference analysis can be a useful tool to improve decisions with regard to selection and controlling for variables in observational studies and avoid potential biases introduced by purely data-driven methods that do not differentiate confounders and mediators [(6)]. Expert knowledge regarding the causal structure of the relationship among diet and physiological risk factors for CVD is warranted.

In this narrative review, we aim to present diagrams illustrating current evidence on the links between diet, as well as conventional and emerging physiological risk factors, with CVD risk, incidence and mortality. To facilitate the visualization of potential causal links (ie., where randomized studies exist) as well as areas for further research, the diagrams displayed information regarding types of studies. The diagrams for conventional and emerging physiological risk factors for CVD was informed by studies included in the British Nutrition

Task Force report on Diet and CVD, which was published in 2019. This report comprehensively reviewed and summarised the state of knowledge on major emerging risk factors for CVD [7]. In addition to extracting key primary and secondary references from this authoritative report, database searches across Medline and Embase were conducted to identify additional studies that might not have been captured by the aforementioned report. Searches were limited to systematic reviews published from 2018 onwards (for search strategy see Appendix A). The diagrams depicting the role of diet in the aetiology of CVD was also informed by the British Nutrition Task Force Report and supplemented by a recent umbrella review [8] and additional relevant studies identified using a key terms approach. This narrative review aimed to present a comprehensive but not necessarily exhaustive view of conventional and emerging risk factors for CVD. The second aim of this paper is to discuss the potential application of the diagrams to studies using tools from causal inference.

Conventional risk factors for CVD

Hypertension and blood pressure disturbances

Figure 1 depicts a summary of the relationships linking markers of hypertension and blood pressure disturbances with CVD outcomes. In terms of observational studies, recent evidence has suggested significant associations between different alterations in blood pressure with increased cerebro- and cardio-vascular risk and events, including increased systolic blood pressure [9], central systolic blood pressure [10] and systolic blood pressure variability [11–15], exaggerated systolic hypertensive response to exercise [16] and orthostatic hypotension [17]. Patients with masked hypertension [18,19] and white coat hypertension [20,21] have also shown increased CVD risk when compared to normotensive patients. One large prospective study in the UK also showed that sustained hypertension has stronger associations with CV events when compared to single blood pressure measurements, but inclusion of long-term systolic blood pressure did not necessarily translate in better performance of CVD prediction tools [22]. The presence of hypertensive disorders during pregnancy [23] have also been associated with increased changes in the vascular structure of the mother, which might contribute to increased CVD risk. Despite the variety of markers considered in systematic reviews of observational studies, only a few of them were explored for their association with CVD mortality. In addition, conclusions drawn from observational studies were often limited by the low number of studies available for

some markers (e.g., blood pressure variability and masked hypertension), the tendency toward publication bias, heterogeneity across studies – which hinders comparability and the lack of proper adjustment for confounders.

In terms of randomized controlled trials (RCTs), recent reviews have shown that compared to standard goals, intensive systolic or blood pressure reduction were accompanied by larger reductions in stroke, coronary heart disease [24], myocardial infarction and major adverse cardiovascular events [25,26]. Intensive reductions in diastolic blood pressure were further associated with reduced CVD mortality (26). However, the benefits of intensive reductions in blood pressure were heterogeneous across different groups. For instance, among patients with type 2 diabetes, data show a linear relationship between systolic blood pressure reduction and the occurrence of stroke [27], but not other CVD events or mortality. Among hypertensive patients with a history of coronary artery disease, lower targets reduced the number of total cardiovascular events, but not adverse events leading to hospitalization, disability or death [28]. Among the elderly, intensive antihypertensive therapy reduced the risk of CVD mortality, but not the risk of stroke [29]. Ultimately, intensive reduction in systolic blood pressure was only beneficial for the prevention of stroke recurrence, but not first occurrence [30].

[Insert figure 1 here]

Diabetes and disturbances in the glucose and insulin metabolism

Diabetes has been associated with increased CVD risk [31]. Indeed, CVD is the most prevalent cause of morbidity and mortality in patients with diabetes [32] thus suggesting an important link between diabetes and CVD. Vascular complications in diabetes might be related to genetic polymorphisms related to nitric oxide production [33]. As demonstrated in figure 2, systematic reviews of observational studies have reported associations between different markers of disturbances in the glucose and insulin metabolism with CVD. Glycemic variability [34] was associated with poorer prognosis in coronary artery disease; fasting glucose [35] with higher risk of major cardiovascular adverse events [36–38]; fasting insulin [39,40] with coronary artery disease, but there was no significant association between HOMA-IR [41] and stroke. Ultimately, an increase in C-peptide levels was associated with a rise in CVD mortality [42].

Different stages and types of diabetes were also associated with increased CVD risk in previous systematic reviews of observational studies, including type 1 diabetes, which was

associated with increased subclinical atherosclerosis [43]; type 2 diabetes with increased risk of stroke, heart failure and occlusive vascular mortality [44–48], with some studies reporting differences between the sexes. For women, having type 2 diabetes was associated with a higher risk for coronary heart disease, stroke, cardiac death and all-cause mortality compared to men with diabetes [49]; Moreover, gestational diabetes was related to increased cardiovascular events postpartum [50] and pre-diabetes was associated with higher risk of major cardiovascular adverse events [35].

Most of the systematic reviews and meta-analyses on this topic were based on observational study designs, and therefore were prone to residual confounding that may affect the associations between diabetes and risk of cardiovascular disease. Furthermore, significant heterogeneity across studies attributable to variability in the measurement of outcomes and adjustment for covariates [34,35,44,45,48,51–53], subgroup comparisons (54), and duration of follow-up [34,55], misclassification of diabetic cases [36,45,56], as well as inconsistencies in defining conventional CVD risk factors [51,52] were observed. Publication bias was found in some of the systematic reviews [34,55,56], and the limited availability of data and/or studies prevented further use of meta-regression analysis [45,51].

Despite the limitations of observational studies, systematic reviews of experimental studies have supported a causal role of pharmacologically mediated glucose control in reducing the risk of non-fatal stroke, non-fatal myocardial infarction, hospitalization for heart failure, major adverse cardiac events [55,57–61], yet intensive glucose reductions did not appear to add extra benefits among type 2 diabetic patients with high risk of CVD [62,63].

Dyslipidemia

Traditional markers of lipid profile, including total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TGL) are well-established risk factors for CVD and are often included in CVD prevention and management guidelines [64,65]. Recent reviews of observational studies have highlighted distinct relationships between these traditional markers and different cardiovascular diseases sub-types. For example, they have reported weak inverse associations between LDL-C levels and haemorrhagic stroke [66], but have not found significant associations between total cholesterol, LDL-C and HDL-C with ischemic stroke [67] or death [68]. In terms of TGL, reviews have shown

detrimental associations between TGL and coronary heart disease [69] and death [68], but mixed associations between TGL and ischemic stroke in Western populations [67–69]. In patients with diabetes the association between TGL and coronary heart disease became insignificant after adjustment for other lipid parameters [69] which was not observed in studies with general population.

As shown in figure 3, it has been suggested that additional lipid-related factors such as inherited lipid abnormalities (e.g., familial hypercholesterolemia), levels of apoliproteins a-1, apoliprotein b, lipoprotein (a) or apolipoprotein E4 isoform should also be considered in CVD risk assessment [70–75]. Familial hypercholesterolemia is a genetic condition that results in elevated LDL-C and potentially increased CVD risk [76]. Recent systematic reviews of observational studies have suggested associations between familial hypercholesterolemia and atherosclerotic cardiovascular disease and non-vascular complications, including increased abdominal aortic aneurysm [77], stroke and peripheral artery disease, with some associations losing significance when analyses were restricted to genetically confirmed cases (e.g., stroke and peripheral artery disease) [77,78]. The certainty of associations was limited by the paucity of studies available worldwide, in particular prospective studies [77]. In addition, the use of data at study-level made it difficult to determine which risk factors were adjusted for in the pooled analysis [63]. In terms of lipoprotein a, a case control followed by meta-analysis supported a causal association between lipoprotein a and the risk of coronary disease [79]. More recently, a review of observational studies reported detrimental associations between lipoprotein a and acute coronary syndrome, acute myocardial infarction, ischemic stroke, but mixed findings related to CVD recurrence and death [80].

In addition to inherited disorders of lipid metabolism, recent advancements in this area include the exploration of the association between non-HDL cholesterol, which has been associated with highest risk of ischemic stroke (but not haemorrhagic) in men [81], increased CVD risk in the general population and individuals with type 2 diabetes, but not with CVD mortality [82]. Non-HDL was also considered a better predictor of coronary heart disease than LDL-C on its own [83]. Moreover, the additional value of the heterogenous population of LDL and HDL-particles (LDL-P and HDL-P) has also been explored. For instance, systematic review reported associations between LDL-P or small LDL particles and CVD risk [84]. In addition, in a meta-analysis of two prospective studies, HDL-C was not associated with atherosclerotic

cardiovascular disease, myocardial infarction or stroke but HDL-P was inversely associated with atherosclerotic cardiovascular disease [85], which was also identified in a previous systematic review of cohorts and case-control studies [86]. An additional meta-analysis of prospective studies has also shown differences in associations between HDL and coronary heart disease (CHD) risk based on ApoC-III binding with HDL [87]. A systematic review of observational studies has described that higher monocyte to HDL ratio on admission in ST-elevation myocardial infarction patients who underwent primary percutaneous coronary intervention was significantly associated with higher major adverse cardiovascular events and in-hospital mortality [88]. More recently, a systematic review of observational and experimental studies has reported negative associations between cholesterol efflux and risk of coronary artery disease or acute coronary syndrome, but not between stroke or myocardial infarction [89]. Reverse cholesterol transport refers to the mechanism by which accumulated cholesterol is moved from the vessel wall to the liver for excretion. An important step in this pathway is cholesterol efflux, by which macrophages within the vessel wall secrete cholesterol outside cells. Moreover, a Mendelian randomization study supported a causal association between remnant cholesterol levels and ischemic heart disease [90], yet only Caucasian subjects were included. Overall, issues related to limited number/quality of studies [67,68], measurement (e.g., single versus repeated measures and fasting versus postprandial) [69,81,82,87] or cut-offs used [68,81,82,88] and adjustment for confounders [67,69,88] were raised as it could impact the strength of the associations between lipid markers and CVD.

In terms of experimental studies, previous systematic reviews have shown that lipid lowering (statins and non-statins) interventions reduce clotting tendency [91], stroke [92], incidence of major cardiovascular events in high risk patients [93], with the reduction of coronary atherosclerosis being associated with reductions in LDL-C and non-HDL-C [94]. Interventions aiming to reduce LDL-C to very low levels showed additional benefits compared to standard targets [95,96] and reduced cardiovascular mortality in patients with higher baseline LDL-C levels [94] — though at the cost of increasing the risk of intracerebral haemorrhage [97], which are perceived to be outweighed by the benefits it promotes on other stroke sub-types [65]. Decisions on the intensity of LDL-C targets should be tailored to individual's CV risk.

[Insert figure 3 here]

Obesity

Figure 4 shows the association between obesity and CVD risk, events and mortality. Different markers of obesity have been associated with increased acute myocardial infarction [98], sudden cardiac death [99,100], stroke [101,102], deleterious vascular outcomes [103] and cardiovascular mortality [104]. For instance, specific adipocytokines, which are biologically active mediators secreted by the adipose tissue, such as adiponectin [105] and visfatin [106] have also been associated with higher coronary artery disease and CVD mortality. In addition, a prospective cohort study of people with obesity and a normal metabolic profile, sometimes referred to as having 'metabolically healthy obesity' showed a substantially higher risk of developing diabetes and atherosclerotic CVD and increased all-cause mortality compared with people with metabolically healthy non-obesity [107]. The increased CVD risk among metabolically healthy overweight and obese could be explained by the high risk of future metabolic dysregulation or obesity-related health consequences [110,112].

Systematic reviews of prospective observational studies have also shown that weight gain was associated with myocardial infarction, coronary heart disease, stroke, and CVD incidence [113]. On the other hand, there is a weight loss paradox in CVD mortality [114–117], which seems to be driven by unintentional weight loss [118]. Limitations of these performed systematic reviews included the fact that the majority of studies used BMI as the only indicator of adiposity/obesity [108,109,120–125]. BMI does not distinguish between weight associated with muscle and weight associated with fat. Furthermore, it does not take into account the difference in fat storage across diverse ethnicities. In some studies, there was no direct measure of body composition [123,126,127], thus, raising concerns regarding the use of convenient indicators of obesity to accurately predict CVD risk. Another important limitation was the lack of adjustment for effect modifiers and confounding factors, such as age, sex, physical activity, smoking status, socioeconomic status and medical treatment [100,112,115,117–119,122,123,126,128–130]. These aspects can influence the meta-analyses results, intervention's impact and must be considered when interpreting the results. In addition, studies that evaluated the influence of genetic aspects did not consider ethnicity or genetic ancestry, thus having implications for generalizing findings [131,132]. Ultimately, sources of bias, including publication bias, small-study effect, evidence of high heterogeneity between studies were also identified. Sources of heterogeneity were often associated with differences in

study characteristics, definitions and measurement of outcomes and sample size, background characteristics of populations from which the studies were derived [108,110,122,133–135].

We also see supportive evidence from Mendelian randomization studies suggesting a causal link between obesity, in particular central obesity, with increased Peripheral Arterial Disease [136], Coronary Arterial Disease [131] and CVD [137,138]. In addition to a possible causal link of central obesity in CVD risk, measures of central obesity, such as waist circumference and waist to hip ratio have also been considered better predictors of CVD risk than BMI [139]. Altough not completely elucidated, different mechanisms have been cited to explain the important role that central obesity plays in CVD, such as promoting insulin resistance, inflammation, oxidative stress which contribute to an atherogenic state [140–142].

Systematic reviews of RCTs have also investigated the impact of weight reducing diets combined or not with physical activity and pharmacological approaches to weight loss. Pharmacological interventions resulted in a significant decrease in CVD mortality [119]. Few studies explored the impact of diet (often low-fat diets) and physical activity and found no significant impact on CVD incidence and mortality. The study was not able to establish whether other forms of diet would provide different results [143], but this will be discussed further in the diet section of this paper. In terms of bariatric surgery, a systematic review found only one RCT that showed no effect of surgery on heart failure incidence [144]. Remaining evidence in this area comes from observational studies [145–147] that show associations among surgery and reduced incidence of heart failure and mortality [148] and coronary artery disease deaths [149] for example. In a number of RCTs, bariatric surgery has also resulted in long term weight reduction, more often driven by reduced food intake, yet additional mechanisms such as gastric emptying and changes in appetite hormones are also involved. RCTs have also reported improvements in other cardiovascular risk factors, such as hypertension, dyslipidemia and type 2 diabetes [150].

Emerging risk factors for CVD

It has been suggested that conventional risk factors for CVD fail to explain at least 25% of new CVD cases, which prompted the interest in exploring the role of emerging risk factors [151]. Despite of criticism [152], studying emerging risk factors for CVD has the potential to contribute to our understanding of the pathophysiological mechanisms of CVD and identify new areas for prevention and targets for treatment [153].

Inflammation

Figure 5 illustrates an increasing interest in the association between inflammation and CVD risk and mortality. Systematic reviews of observational studies have shown that systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and ankylosing spondylitis are associated with increased subclinical atherosclerosis and risk of developing cardiovascular disease [154–157]. In addition, endometriosis, also considered an inflammatory disease, has also been associated with increased risk of lifelong cardiovascular events including myocardial infarction, independent of demographic and lifestyle factors [158]. Localised inflammation has also been linked to vascular pathology. For instance, a meta-analysis of observational studies revealed a significant relationship between periodontitis and peripheral arterial disease [159]. Ultimately, inflammation triggered by pathogens has also been linked to increased risk of cardiovascular and cerebrovascular events, specifically infections with *H. pylori, C. pneumonia and M. pneumonia* [160].

Different markers of inflammation have been associated with increases CVD risk, yet not all of the identified relationships were proved to be causal. For instance, a reliable marker of systemic inflammation, C-reactive protein (CRP) and high-sensitivity C-reactive protein (hs-CRP) were associated with increased risk of major cardiovascular events among patients with peripheral artery disease in systematic reviewand meta-analysis observational studies [161,162], with increased risk of in-hospital mortality in patients with aortic dissection [163] and with cardiovascular and all-cause mortality in type 2 diabetes patients – this result was independent of study design, follow-up duration of the patients or the presence of pre-existing cardiovascular risk factors [164]. Despite supportive evidence from observational studies, a Mendelian randomization study has reported that variation in hs-CRP was not associated with CVD [165], suggesting that hs-CRP might be a risk marker but not a risk factor. Additional markers further explored include: monocyte chemoattractant protein-1 or intercellular adhesion molecule 1, which is a marker of vascular inflammation that has been correlated with ischemic stroke, coronary artery disease and myocardial infarction [166,167]; erythrocyte distribution width (RDW), which is a novel prognostic marker that may reflect an underlying inflammatory state, was shown to predict adverse outcomes in CVD patients [168]. Neutrophil-to-lymphocyte ratio (NLR), which identifies subclinical inflammation, was identified as a predictor of hospitalization and

long-term prognosis in patients with ST-elevation myocardial infarction after percutaneous coronary intervention [169].

Inflammation-associated immune response also seems to play a critical role in CVD progression. Proinflammatory cytokines T helper cell 1 (Th1) and T helper cell 2 were positively linked with retinopathy and cardiovascular complications [170]. One of the most important pro-inflammatory cytokines, tumour necrosis factor-alpha (TNF-α) was shown to contribute to extensive arterial disease [171]. Moreover, upregulation of the TNF- receptors 1 and 2 was positively associated with CVD events and mortality in patients with type 2 diabetes [172].

Myeloperoxidase, a white blood cell-derived enzyme that quantifies inflammatory activity from the luminal aspect of the arterial wall, was shown to be positively associated with increased risk of mortality in patients with systemic CVD, but not associated with myocardial infarction or major adverse cardiac events [173]. Serum amyloid A, an acute-phase protein involved in the pathogenesis of atherosclerosis, was associated with increased risk of coronary heart disease, especially for patients aged more than 55 years [174]. Systematic reviews of observational studies have shown that IL-6 is present at higher circulating levels in CVD patients than in non-CVD controls [175]. In addition, a Mendelian randomization study indicated that genetic variants which lead to higher circulating concentrations of IL-6 receptors (IL-6R) (and consequently less IL-6 cell signalling and lower circulating CRP) appear to be protective against CHD [176].

RCTs have shown mixed results on the impact of anti-inflammatory therapies with non-TNF targeting biologics and small molecules approved for the treatment of inflammatory arthritis such as tocilizumab, abatacept and anakinrarender atherosclerosis, stroke, myocardial infarction, cardiovascular death [177]. Although it has been hypothesized that groups of patients who have a significant inflammatory component contributing to their cardiovascular disease might benefit from anti-inflammatory strategies [178], such evidence comes mostly from observational studies. It has been suggested that different immunomodulatory treatments might be needed for different atherosclerotic stages [179] but more studies are necessary to determine specific targets that contribute to increased CVD risk in patients with local and systemic inflammation.

Oxidative Stress

Most of the evidence linking oxidative stress to CVD comes from observational studies. In systematic reviews, ox-LDL levels were associated with carotid plaques, carotid media thickness and atherosclerotic cardiovascular disease, yet associations were not consistent across studies [(180)]. In addition, a review of prospective studies showed that IgM anti-oxLDL antibodies offer some protection from more severe CAD and possibly cardiovascular events [(181)]. Emerging evidence from one systematic review further linked Oxidative Balance Scores (OBSs), which evaluate the global balance of individuals' oxidation-reduction status, with CVD risk [(182)]. Additionally, a critical review suggested that NADPH oxidases might play an important role in cardiovascular disease occurrence and development [(183)]. In terms of experimental studies, a recent systematic review of randomized studies showed that addition of oxidase inhibitors (XOIs) to conventional ACE-inhibitors may potentially result in improved survival free from major adverse cardiovascular events in post-acute myocardial infarction patients [(184)].

Haemostatic and fibrinolytic disturbances

The haemostatic system prevents bleeding and haemorrhage following any form of injury to the endothelium. In the context of CVD, the rupture of the atheromatous plaque triggers coagulation processes within the arterial lumen, which leads to thrombus formation and blood clot obstructing blood flow thereby causing tissue death [(185)].

As shown in figure 7, several markers of coagulation processes have been studied in recent years. For instance, a recent meta-analysis of prospective studies followed by a Mendelian randomization study identified 13 genetic loci with modest contributions to plasma levels of FVIII or vWF [(186)], which have also shown to be associated with the risk of venous thromboembolism [(186)], coronary artery and heart disease [(187,188)] and major adverse cardiovascular events [(187)]. For fibrinogen, a systematic review of prospective studies reported that fibrinogen levels improved CVD risk prediction in men but not in women [(189)]. However, a more recent meta-analysis of prospective studies showed that there was no evidence for a causal role of fibrinogen in coronary artery disease, stroke, and venous thromboembolism [(190)]. Tissue plasminogen activator (t-PA) is a thrombolytic protease produced mainly by vascular endothelial cells, that converts inactive plasminogen into active plasmin, which then degrades fibrin complexes, a major component of a thrombus. A review of prospective studies showed that t-PA

antigen was log-linearly related to coronary heart disease risk [188]. In addition to t-PA, D-dimer and VWF were more weakly associated with incident coronary heart disease than markers of inflammation (IL-6 and PCR) and lipid metabolism (TGL, Lp(a) and total cholesterol) in a systematic review of prospective studies, markers of coagulation [188]. Observational associations between coagulation markers and CVD risk were limited by a number of factors, including small number os studies available, incomplete information [187,189] and measurement issues (e.g., diurnal or seasonal fluctuations) [187,189], and measurement issues [188].

In contrast to t-PA, plasminogen activator inhibitor-1 (PAI-1) is a member of the serine protease inhibitor family which inhibits fibrinolysis. The thrombosis process is determined by the balance between t-PA and PAI-1, with increased PAI-1 levels in plasma inducing a hypercoagulable state [193]. Systematic reviews have shown that PAI-1 levels were an independent predictor of a first CVD event among individuals with no prior CVD [194]. Furthermore, elevated PAI-1 antigen levels were associated with major adverse cardiac events (death, myocardial infarction, and cerebrovascular events including stroke and transient ischemic attacks) in populations with and without established CVD. In addition, elevated PAI-1 antigen levels were associated with all-cause mortality [195]. Another study, using observational data and a Mendelian randomization, has shown the causal effect of PAI-1 on CHD onset, potentially mediated by blood glucose dysfunction, suggesting that the fibrinolysis pathway may be a good target for CHD treatment [196].

In terms of experimental studies, recent systematic reviews of RCTs have shown that different anticoagulant therapies (factor Xa inhibitors such as apixaban, edoxaban, and rivaroxaban) reduced the occurrence of ischemic stroke [197,198] and its severity [199], of embolism [192,200,201] and of major adverse cardiovascular events [202]. Factors such as individual's age, body mass index could modify the treatment effect of anticoagulation but was not explored in all studies for anticoagulation therapies.

The link between risk factors and endothelial dysfunction, an intermediary marker of CVD

The vascular endothelium plays a vital role in the pathogenesis of cardiovascular disease. We found evidence linking conventional CVD risk factors, such as hypertensive disorders [23], obesity and diabetes [203] to systemic endothelial dysfunction, leading to CVD. Chronic diseases such as non-alcoholic fatty liver disease have also been associated with an increased risk of

atherosclerotic cardiovascular disease, in a mechanism involving endothelial dysfunction [204]. Albuminuria, which is an early marker of kidney disease, has also been associated with cerebral small vessel disease, which makes it particularly important as a biomarker in the evaluation of brain microvascular damage [205]. The release of endothelial cell-derived substances such as nitric oxide, a potent vasodilator, contributes to vascular health. A non-invasive method of assessing endothelial function in peripheral vessels is the brachial artery flow-mediated dilatation (FMD) [206].

During the test, a rapid decrease in blood flow is induced by inflating an arm cuff to supra-systolic pressure for 5 min. This ischaemic period results in increased production of nitric oxide and other vasoactive molecules from the endothelial cells. Upon pressure release, the increase in flow known as hyperaemia that induces shear stress, results in vasodilatation mediated by nitric oxide diffusing into the vascular smooth muscle cells. These changes can be monitored in real time using a Doppler ultrasound. Therefore, brachial artery FMD is considered a measure of endothelium- and nitric oxide-dependent vasodilation [207]. Several meta-analysis suggested that impairment of brachial FMD is significantly associated with future cardiovascular events [208–210]. The strength of association of FMD and future CVD events was found to be higher in patients with established CVD, suggesting that FMD may be more useful in screening for recurrent CVD events in patients at high risk [211].

Recent advances in this area have also highlighted a shared mechanistic pathway involving inflammation and endothelium oxidation in endothelial dysfunction [212,213]. For instance, SNPs involved in processes related to endothelial and vascular health such as vascular endothelial growth factor receptor, platelet/endothelial cell adhesion molecule-, endothelial nitric oxide synthase and endothelin-1 contribute to local and systemic vascular disorders [214–218], yet studies had small sample sizes, were limited in number or did not account for gene-environment interaction.

The carotid intima-media thickness (CIMT) is used to diagnose the extent of carotid atherosclerotic vascular disease by using ultrasound which measures the thickness of the inner two layers of the carotid artery—the intima and media. CIMT changes precede plaque formation in carotid atherosclerosis, so this non-invasive measurement can accurately describe the process of arterial wall changes due to atherosclerosis and can be used to monitor apparently healthy and at-risk populations [220]. Systematic review and meta-analysis have also established that increased

CIMT is a reliable marker of the progression of coronary artery disease, increased risk of stroke in older adult without a history of cardiovascular disease, cerebral infarction, atherosclerosis throughout the body [221]. Furthermore, increased CIMT was shown to be an independent predictor of myocardial infarction and CVD [222]. Several other longitudinal studies showed that CIMT measurements are a validated surrogate end point for atherosclerosis and vascular disease risk, suggesting that CIMT can provide additional information that cannot be obtained based on the assessment of conventional cardiovascular risk factors alone [223].

The interconnections between CVD risk factors

Intergenerational perspective

The hypothesis that foetal, infant and childhood conditions affect CVD risk later in life is not new [224]. In recent years, systematic reviews of observational studies provided an indication that exposure to famine (particularly when coupled with exposure to nutritional excess after birth), higher maternal weight [225], maternal diabetes [226], maternal dyslipidaemia [227], maternal hypertension [228], maternal polycystic ovarian syndrome [229] were associated with offspring's risk of congenital heart defects, CVD events and risk. There is also indication that low birth weight and prematurity are associated with greater CVD and CV event risk [230,231]. Some researchers also hypothesize that adverse intrauterine conditions result in both structural changes in the organs along with increased risk of metabolic disturbances, such as obesity, hypertension, diabetes, dyslipidemias, all of which impact CVD risk [232]. As presented in figure 9, the majority of the evidence on the role of fetal and childhood conditions comes from observational study designs, meaning that residual or unmeasured factors may confound the association between fetal and childhood conditions with future CVD risk. In addition, study heterogeneity, which in some cases prevented meta-regression analysis [233], recall bias [234], selection bias, citation bias [235] and short follow-up, which prevented further stratified analysis or subgroup comparisons such as sex- or age-specific relationships [225,236] in future CVD risk, were important limitations. A small number of intervention studies have supported that macro- and micronutrient supplementation in mothers during the antenatal period resulted in lower incidence of T2D and hypertension in childhood, but longer follow-up is still needed [237,238].

Integration of multiple biological pathways

We find many examples that illustrate how multiple physiological pathways are integrated in CVD risk. For instance, one previous Mendelian randomization study with 90.000 Danish individuals suggested that the relationship between obesity and ischaemic heart diseases was partly mediated through non-fasting remnant cholesterol (7%), which is the cholesterol content of triacylglycerol-rich lipoproteins, low-density lipoprotein cholesterol (8%) and elevated blood pressure (7%) [(239)]. A more recent two-sample Mendelian randomization study with a larger number of participants also supported the involvement of triacylglycerol levels and further identified an important role of poor glycaemic control on the risk of coronary heart diseases [(240)]. Body composition changes typical of obesity (e.g., visceral fat and ectopic fat), as well as pro-inflammatory cytokines produced by the adipose tissue, might influence CVD risk via the mechanisms related to changes in lipid profile (e.g., LDL-C, HDL-C, triglycerides and remnant cholesterol), insulin resistance, hypertension, but also through pro-inflammatory (e.g., increase in TNF-alpha and IL-6), pro-thrombotic (e.g., increase in PAI-1) and pro-oxidative states (e.g., Ox-LDL, NADH and ROS) [(239–242),] as well as through hemodynamic and structural changes of the heart, and cardiac functions [(243)].

Obesity is not the only component interacting with other risk factors for CVD risk. For instance, a recent umbrella review has supported a causal role of higher birth-weight, BMI, waist circumference and systolic blood pressure for diabetes risk [(244)], which have been discussed in previous sections of this paper as being a relevant risk factor for CVD. In addition, a Mendelian randomization study have supported the existence of shared genes between type 2 diabetes and coronary heart disease, yet mediation analyses are still needed to disentangle the effects of type 2 diabetes from those related to obesity in the context of CVD risk [(245)].

The role of natural and built human environments

Beyond interactions between genes and physiological systems, characteristics of the human environment directly or indirectly might affect CVD risk, such as circadian rhythms, seasons of the year, sunlight exposure, altitude, noise, pollution, green spaces, socioeconomic deprivation, social networks, nutrition and physical activity [(246)]. For example, exposure to air pollution, might contribute to increased CVD risk via increased oxidative stress, followed by increased inflammatory and coagulation responses, which impact atherosclerosis, vascular and endothelial functions [(247)]. Exposure to air pollution might be particularly worrisome for

susceptible individuals, such as those with underlying atherosclerosis (or predisposing conditions), who are at higher risk of cardiovascular event or deaths in response to pollution exposure, when compared with those who are otherwise healthy [247]. Thus, understanding how different characteristics of human environments, including diet, interact with physiological systems and affect CVD risk is necessary to improve CVD prediction and management.

The role of diet on CVD risk

Nutrient-based approach

Diet is one component that moderates or amplifies CVD risk. As presented in figure 10a, more robust evidence around macronutrients and CVD risk is available for the role of dietary fats, potentially due to the established relationship between circulating cholesterol levels and cholesterol lowering interventions on CVD risk [248]. However, evidence on the role of dietary cholesterol has been mixed. For instance, one systematic review and meta-analysis of cohort studies found that cholesterol intake was not associated with coronary artery disease, ischemic stroke, or hemorrhagic stroke [249]. On the contrary, a more recent meta-analysis of prospective studies in the US found that a higher intake of dietary cholesterol was associated with a higher risk of CVD incidence and mortality [250]. In addition, evidence to date is not supportive of a link between total fat intake and risk of coronary heart disease or CVD mortality. For specific lipid components, such as saturated fat, current observational studies do not show a relationship with coronary heart disease or CVD mortality either – the only exception seems to be a relationship with the incidence of ischemic stroke. More consistent findings exist on the association between trans fatty acids and coronary heart disease and CVD mortality, thus justifying calls for trans-fat ban [251]. In experimental studies, total intake of polyunsaturated fatty acids is also not associated with coronary heart disease or CVD mortality and conflicting evidence remains on individual associations between n-3 and n-6 polyunsaturated fatty acids.

In 1953, a high intake of n-3 polyunsaturated fatty acids (n-3 PUFA) in the Greenland Eskimo population was associated with a relatively low incidence of CHD and since then there is growing interest in the use of n-3 PUFA as therapeutic agents in CVD [252]. Most well-known sources of n-3 PUFA are marine based fish and fish oil that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In reviews of prospective studies, increased n-3 PUFA intake was associated with a lower risk of fatal myocardial infarction or major cardiovascular events [253,254], yet mixed findings emerge from RCTs [8]. Despite that, there is strong evidence from

RTCs that replacing saturated fatty acids (commonly found in animal-based foods like butter, cheese, fatty meat) with n-3 PUFA reduces the risk of CVD events and coronary mortality [255]. The link between n-3 and CVD can be explained by the cardioprotective actions attributed to n-3 PUFA in mechanisms involving anti-inflammatory, antiatherogenic, antiarrhythmic, antithrombotic and antioxidant functions [256].

More recently, increased attention has been paid to the relevance of other macronutrients, such as carbohydrates and proteins on CVD incidence [257]. Similar to the evidence on fats, total intake of carbohydrates was not associated with CVD incidence and mortality as shown in a meta-analysis of large prospective studies conducted in North America and Europe [258]. Rather, evidence to date suggests that the quality of carbohydrates might be more important over quantity. There is supporting evidence on the role of dietary fibre, with prospective studies and RCTs reporting associations between fibre intake and improvements in a number of physiological CVD risk factors [259] and coronary heart disease and CVD incidence [260].

Figure 10b shows that a number of micronutrients have been tested in experimental studies for their potential role in CVD prevention. There are a number of studies that refute benefits of single nutrients, such as from vitamin D and C, on CVD risk, major adverse events and mortality [261]. However, there is some supportive evidence of a potential benefit of folic acid and B vitamins in stroke and CVD prevention [262]. In addition, a recent Mendelian Randomization study showed that genetically predicted vitamin E levels were associated with small protection in terms of coronary artery disease and myocardial infarction, which could be potentially related to shared genetic pathways between vitamin E and lipids metabolism [263].

Food based-approach

In recognition that individuals eat whole foods and not isolated nutrients, studies have also explored the role of specific food groups or individual foods on CVD risk, which are depicted in figure 10c. For instance, a recent systematic review of observational and experimental studies showed that, olive oil, which is high in monounsaturated fatty acids, was associated with decreased risk of stroke, but not coronary heart disease. Also, in observational studies, consumption of nuts, which are high in polyunsaturated fats, were associated with both, reduced coronary heart disease and stroke (8). Also, foods that are high in simple carbohydrates, such as sugar-sweetened beverages, were associated with increased coronary heart disease incidence in previous meta-analysis of prospective studies (264) and whole grains, which are

high in complex carbohydrates, were associated with decreased CVD mortality and risk of coronary heart disease, but not stroke (8).

In terms of protein rich foods, such as meat, fish, legumes and dairy it might be difficult to disentangle the effect of any particular nutrient on CVD risk, incidence or mortality. For instance, although higher total protein intake has been associated with a higher risk of CVD mortality and non-stroke CVD mortality in a recent meta-analysis of prospective studies (Figure 10a), this association was mainly driven by animal protein sources, rather than plant-based sources (Figure 10c). A detrimental effect of animal protein was only observed in North America and Europe, but not in Japan [(265)], suggesting that pathways linking animal protein and CVD mortality might be related to nutrients (e.g., saturated fats) other than protein content that are present in animal foods. For instance, fish was associated with reduced CVD mortality in observational studies [(8)]. For legumes, which are rich not only in protein but also in fibre, a review of observational studies showed associations between intake and reduced coronary heart disease risk, CVD mortality, but not stroke [(8)]. In terms of dairy, a recent overview of systematic reviews showed that in observational studies consumption of total dairy was associated with risk of stroke, but not consistently associated with CVD, coronary heart disease or myocardial infarction risk. When looking at specific dairy foods, yoghurt or buttermilk were not significantly associated with CVD, coronary heart disease or stroke, while fermented milk showed benefits in terms of CVD, coronary heart disease and stroke incidence and mortality, and milk and cheese showed mixed findings for all CVD outcomes [(266)], thus highlighting that particular fermented dairy products might be of relevance.

Other foods, such as fruits and vegetables, were associated with decreased risk of stroke, but did not decrease the risk of coronary heart disease and CVD mortality [(8)] – which might be potentially linked to the fibre and specific minerals content. Cacao, coffee and green tea are recognized by their phytochemicals content, which is hypothesized to exert CVD protection. In systematic reviews of observational studies, chocolate reduced coronary heart disease, stroke, and CVD mortality, coffee was only associated with CVD mortality and green tea with reduced the risk of stroke [(8)]. In addition, we found emerging evidence from a systematic review of cross-sectional and prospective studies demonstrating that a high intake of ultra-processed foods is associated with increased risk of CVD and cerebrovascular disease [(267)].

Dietary-pattern approach

To account for the cumulative effect of and interactions between nutrients and foods on health outcomes [268], analysis of the impact of dietary patterns on CVD are becoming more common in nutrition research (presented in figure 10d). In systematic reviews of RCTs, consumption of healthy diets, classified using the Healthy Eating Index (HEI), for example, have resulted in reduced CVD risk in high risk populations, yet no benefits in CVD mortality for the general population were observed [8]. In addition, the Mediterranean diet, which is composed mostly by fruits, vegetables, whole grains, legumes and beans, olive oil and nuts, with moderate amounts of animal proteins, resulted in reduced the risk of myocardial infarction, stroke and CVD incidence/mortality in RCTs, with mixed findings on coronary heart disease [8,269]. Associations with carotid intima-media thickness, which is an established surrogate marker of preclinical atherosclerosis, still need to be confirmed, as discussed in a systematic review of cross-sectional studies and RCTs [270]. Another dietary pattern that also showed promising results in terms of CVD prevention is the Dietary Approaches to Stop Hypertension (DASH). Similar to the Mediterranean diet, the DASH diet is also focused on fruits and vegetables, and whole grains. Protein sources include low-fat dairy, fish, poultry and nuts, while red meat is also limited. DASH also reinforces foods that are high in potassium, calcium, and magnesium and low in sodium. An umbrella review of prospective studies showed that consumption of the DASH diet decreased the incidence of cardiovascular disease, coronary heart disease, stroke [8]. DASH diet was also associated with reductions carotid media thickness [270]. Comparisons between the DASH diet and the Mediterranean show that the DASH diet is more effective in reducing blood pressure, with more pronounced benefits observed among individuals with larger reductions in body weight [271]. The Mediterranean diet, on another hand, has less consistent evidence in terms of systolic blood pressure, diastolic blood pressure, triglycerides, HDL-cholesterol, insulin, HbAc1and LDL-C, but more consistent results in terms of body weight/fat, total cholesterol, glucose and C-reactive protein [269]. Ultimately, adherence to the Japanese diet consisting of eight components (high intake of rice, miso soup, seaweeds, pickles, green and yellow vegetables, fish, and green tea; low intake of beef and pork) has also been associated with a decreased risk CVD mortality among adults living in multiple areas across Japan [272]. To date, Paleolithic diet [273] and Nordic diet [274] were associated with physiological risk factors for CVD, but not CVD clinical endpoints.

In addition to the more comprehensive dietary patterns which provide recommendations and targets for various food groups, there are diets that focus on the exclusion of specific food groups, such as the low(er) carbohydrate or vegetarian diets. Systematic review of observational studies showed that high adherence to a vegetarian diet was associated with reduced coronary heart disease, with no reported impact on stroke or CVD mortality [8]. In similar studies, low carbohydrate diets were not associated with reductions in risk of CVD incidence or mortality [275], yet RCTs reported improvements in traditional risk factors for CVD [276]. In diets that are focused on the exclusion of particular food groups, careful consideration of replacement or substitute food groups is required. For instance, a meta-analysis of prospective studies showed low carbohydrate diets were associated with increased mortality when carbohydrates were exchanged for animal-derived fat or protein; and decreased when the substitutions were plant-based fats or proteins [277]. Low carbohydrate diets can also result in reductions or elimination of whole grains or fibres, which, as previously described, have shown cardioprotective benefits.

From the evidence presented, we tentatively conclude that different dietary factors impact CVD risk via different pathways. Diets should be considered in the context of the nutrients they encompass and interventions to address CVD risk should be seen in the context of individuals/populations being treated, which have implications for both research and practice.

[Insert figure 10 here]

Innovation in future research

As RCTs are difficult to perform, time consuming and not meant to answer all questions regarding the role of diet in CVD incidence and mortality, epidemiological research must not only recognize that different dietary patterns impact CVD risk via different nutrients and physiological pathways but also to pursue innovative efforts to properly address the complexities that are inherent to both domains.

A new research direction in nutrition science include the use of causal inference thinking and analytical methods (e.g., matching, inverse probability, G-estimation). Three key conditions required to enable causal inferences to be made from observational data, include consistency (ie., the values of treatment under comparison correspond to well-defined interventions), exchangeability (ie., probability of receiving every value of treatment depends only on measured covariates) and positivity (ie., the probability of receiving every value of treatment is greater than zero) [278]. Causal inference thinking and analysis aims to emulate a randomized experiment and

extract evidence for cause-and-effect relationships by investigating well-defined interventions [279] and counterfactual scenarios from observational studies [280–283]. For example, in a causal inference study, researchers pose questions such as "what is the impact of diet X on cardiovascular risk Y?" and draw structural relationships between exposures and outcomes, taking account of confounders and mediators. Subsequently, observational data is used to corroborate or invalidate these relationships. Unlike standard statistical approaches, causal inference analysis allow not only the pathways to be inferred from the data, but also the nature of the functional relationships among risk drivers and outcome variables. These techniques address a common problem in epidemiological research where highly non-linear relationships cannot be captured properly with standard statistical approaches that typically assume linear or log-linear relationships and make strong assumptions with respect to the behaviour of residuals.

Considering the complexity of biological processes and their interactions with built and social environments, substantial challenges remain before we can robustly establish cause and effect from observational data. Expert knowledge of the causal structure underlying diet and health issues remains a crucial component in causal inference analysis and interpretation [284]. The diagrams included in this paper present an alternative way to consolidate and better visualise available evidence. For instance, the diagrams provide information of the type of evidence supporting the link between a number of variables and CVD outcomes, thus highlighting which of these are potential risk factors for CVD (e.g., consistent evidence from randomized studies). Altough the diagrams are currently presented as separate figures, future developments include their integration into an interactive platform that would enable researchers and clinicians to appreciate the complexity of questions linking diet and CVD outcomes and better design causal diagrams, which are considered useful tools for identifying, measuring and addressing potential counfounders [285]. Future developments in this area also include the use of more extensive datasets.

In addition, the area of precision nutrition also deserves further exploration as individual's responses to diets may vary based on their phenotype or 'metabotype' (which has a multitude of determinants not fully understood yet)[286]. One large prospective study, followed by a randomized trial, showed that the use of an algorithm that integrated blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota information accurately predicted and improved individual's glycemic responses to a nutrition intervention [287]. The exploration of

phenotypic factors that influence response to nutrition interventions remain largely unexplored and could further improve the understanding of nutrition intervention results [288].

Implications for evidence-informed practice

Current clinical practice addressing cardiovascular disease blends the interaction between population research with the individual the clinician is caring for. Managing CVD risk is started by modifying lifestyle factors in the first instance followed by introducing medication, for treating hypertension, diabetes mellitus type 2 and hypercholesterolaemia. However, guidelines for how to help patients change their lifestyle are lacking for medical professionals who often rely on the use of knowledge from very limited training in medical schools, or their own research [289].

One reason guidelines may be lacking for clinicians to give advice on lifestyle change is the recognition that generic advice which is effective and safe is not often possible for the whole population. In terms of diet, consideration of the trade-offs in terms of risks/benefits must be considered in the context of individual CVD risk profiles, along with factors such as accessibility and long-term feasibility. As such, clinicians must identify and tailor advice to achieve success. However, with the dawn of precision nutritional care, algorithms or guidelines for specific sub-sets of the population may be possible to create, allowing clinicians to feel more comfortable initiating lifestyle changes tailored to the individual . One challenge is that precision medicine is difficult to deliver in primary care. Another challenge lies in doing more extensive and more rigorous research to create robust algorithms to support effective personalised care using objective health risk scoring methods that seamlessly incorporate diet and lifestyle related risk factors amongst others. This would entail using blood samples from hundreds of thousands participants to create a dataset that can be compared and ultra fast computers to process this data in depth, enabling the development of algorithms that are more adaptable and effective for each individual. Dealing with confounders becomes even more important when developing guidelines for personalised interventions.

Conclusion

Current evidence from observational studies regarding the role of blood pressure disturbances suggests that less understood disorders such as white-coat hypertension, masked hypertension (normal blood pressure reading in the clinic but elevated during ambulatory measurements), orthostatic hypertension as well as pre-eclampsia are not completely benign in terms of CVD risk. In experimental studies, not all groups of hypertensive patients and not all CVD outcomes benefited from intensive reductions in blood pressure. Similarly, several markers of disturbances in the glucose and insulin metabolism have been associated with increased risk of particular CVD events and/or mortality. Early stages of diabetes including gestational diabetes were also linked with increased CVD events, potentially due to increased risk to develop type 2 diabetes in the long-term. Reducing glucose levels below standard targets showed no benefits for patients with type 2 diabetes and high risk of CVD, yet studies in the primary prevention context are still needed. Although conventional lipid markers such as LDL-C, HDL-C, TGL have been largely associated with overall CVD risk, for particular CVD outcomes, the evidence is less consistent, such as ischaemic stroke. More recent evidence in this domain points to the relevance various apolipoproteins, and of more specific components, such as proteins binded to cholesterol or cholesterol sub-particles. Different from intensive reductions on glucose levels, reducing LDL-C below standard targets were associated with increased reductions of CVD events among high risk patients, at expense of increased risk of intracerebral haemorrhage. For obesity, different markers that suggest accumulation of adipose tissue, as well as substances secreted by adipocytes, were associated with increased CVD events and a few of them with increased CVD mortality. RCTs of pharmacologically induced weight loss demonstrated reduced CVD mortality, yet evidence of other approaches such as low-fat diets and bariatric surgery is still limited. Although there are several emerging markers of disturbances in blood pressure, glucose and insulin, lipids and fat deposition, the utility of including such markers in CVD prediction tools or targeting them in CVD prevention therapies remains unknown. Also, considering that the benefit of targets above the usual standards were heterogeneous across different groups of patients, suggests that future studies should be sensitive to the background risk of patients and the relevance of other factors in CVD risk. Ultimately, future studies should also consider the specific mechanisms of different CVD diseases, as both established and new markers of blood

pressure, glucose and insulin metabolism, lipid metabolism and fat deposition were associated with some CVD outcomes but not others.

Evidence regarding the role of more emerging risk factors, such as inflammatory conditions, relies mostly on observational studies that highlight different inflammatory diseases and markers associated with increased CVD risk, yet more studies are still required to determine causal relationships and specific targets for treatment. On the contrary, there are several experimental studies showing benefits of anti-coagulation therapies for CVD, yet many coagulation markers still need to be explored for causality. Ultimately, evidence regarding the role of endothelial dysfunction, which has been considered an important mediator between other risk factors and CVD events, also relies on observational studies and further exploration is still required.

This review also highlighted additional factors that might influence CVD risk through the previously discussed physiological risk factors, including pre-birth and early childhood conditions, yet evidence also relies on observational studies which are subject to several confounders. Intervention studies were scarce potentially due to long-term follow-up required to observe the impact on CVD clinical outcomes. Although not extensively, we also presented additional factors such as those related to the environment which might influence CVD risk, such as air pollution, socioeconomic deprivation, and diet in particular.

In terms of diet, many aspects might impact cardiovascular health. Although network analysis suggests superiority of particular dietary patterns over others, which might be related to the cumulative effect of various nutrients on different risk factors for CVD, different results still present for different individuals, irrespective of adherence issues. In order to move forward and disentangle the effect of diet on CVD, the scientific community should consider the multifactorial nature of CVD and the complex interplay between physiological conventional and emerging risk factors with natural and built environments, while bringing the life course and the role of additional environmental factors into the spotlight. In order to bring together the different confounders that would account for biased estimates in observational studies, nutrition research would benefit from large collaborations and virtual tools that organise information and data across the different pathways that lead to CVD. Experimental research would benefit from exploring the impact of diet on physiological and conventional to novel and emerging risk factors linked to CVD as part of a continuum where the interplay between individual risk factors

needs to be better understood and where possible, quantified. Whilst the challenge in translating results from controlled environments to real-life contexts remains, further research strategies are needed to systematically harness routine 'real-world' data such as those from electronic health records and take a causal inference analysis approach to investigating temporal and aetiological factors highlighting previously underutilised opportunities for risk mitigation particularly through the modulation of diet and lifestyle factors.

Acknowledgements: We would like to acknowledge Mary Ward and Luigi Palla for commenting on the relevance of this manuscript and Nate Jensen for contributing to the broader Causal Inference Project.

Financial support: The Swiss Re Institute and Core Funding to the NNEdPro Nutrition Research and Innovation Consortium

Conflict of interest: no conflict of interest to declare

Authorship: MRLV was responsible for the project administration, as well as conceptualization, data curation and analysis and writing the original draft of the manuscript. LB, CGM, CRT, SKK, AK and SA contributed to the conceptualization, data curation and analysis, and writing the original draft of the manuscript. SM and XD contributed to writing the original draft of the manuscript. RG, DU, JB and LG contributed to reviews and editing. SR and RG were responsible for the supervision, review and edits, and funding acquisition.

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology [Internet]. 2020 Dec 22 [cited 2021 Aug 25];76(25):2982. Available from: /pmc/articles/PMC7755038/
2. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. The Global Economic Burden of Noncommunicable Diseases. Geneva; 2011.
3. United Nations. Transforming our world: The 2030 agenda for sustainable development. 2015.
4. World Health Organization. Heart. Technical package for cardiovascular disease management in primary health care [Internet]. Geneva; 2016 [cited 2021 Aug 25]. Available from: https://www.who.int/cardiovascular_diseases/hearts/Hearts_package.pdf
5. VanderWeele TJ. Principles of confounder selection. European Journal of Epidemiology. 2019 Mar 15;34(3):211–9.
6. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. Vol. 8, BMC Medical Research Methodology. BioMed Central; 2008. p. 70.
7. Stanner S. Cardiovascular disease : diet, nutrition and emerging risk factors. Second edition.. Stanner S, Coe S, Frayn KN (Keith N), editors. 2019. (British nutrition foundation).
8. Chareonrungrueangchai K, Wongkawinwoot K, Anothaisintawee T, Reutrakul S. Dietary Factors and Risks of Cardiovascular Diseases: An Umbrella Review. Nutrients [Internet]. 2020 Apr 15;12(4):1088. Available from: https://www.mdpi.com/2072-6643/12/4/1088
9. Pan H, Hibino M, Kobeissi E, Aune D. Blood pressure, hypertension and the risk of sudden cardiac death: a systematic review and meta-analysis of cohort studies. European journal of epidemiology. 2019 Dec;
10. Li W-F, Huang Y-Q, Feng Y-Q. Association between central haemodynamics and risk of all-cause mortality and cardiovascular disease: a systematic review and meta-analysis. Journal of human hypertension. 2019;33(7):531–41.

11. Appiah KOB, Patel M, Panerai RB, Robinson TG, Haunton VJ. Increased blood pressure variability following acute stroke is associated with poor long-term outcomes: a systematic review. Blood pressure monitoring. 2019 Apr;24(2):67–73.
12. Wang H, Li M, Xie S-H, Oyang Y-T, Yin M, Bao B, et al. Visit-to-visit Systolic Blood Pressure Variability and Stroke Risk: A Systematic Review and Meta-analysis. Current medical science. 2019 Oct;39(5):741–7.
13. Chiriacò M, Pateras K, Virdis A, Charakida M, Kyriakopoulou D, Nannipieri M, et al. Association between blood pressure variability, cardiovascular disease and mortality in type 2 diabetes: A systematic review and meta-analysis. Diabetes, obesity & metabolism. 2019 Dec;21(12):2587–98.
14. Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, et al. Association Between Blood Pressure Variability and Cerebral Small-Vessel Disease: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2020 Jan;9(1):e013841.
15. Ma Y, Song A, Viswanathan A, Blacker D, Vernooij MW, Hofman A, et al. Blood Pressure Variability and Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis of Population-Based Cohorts. Stroke. 2020;51(1):82–9.
16. Perçuku L, Bajraktari G, Jashari H, Bytyçi I, Ibrahimi P, Henein MY. Exaggerated systolic hypertensive response to exercise predicts cardiovascular events: a systematic review and meta-analysis. Polish archives of internal medicine. 2019;129(12):855–63.
17. Min M, Shi T, Sun C, Liang M, Zhang Y, Tian S, et al. The association between orthostatic hypotension and cognition and stroke: a meta-analysis of prospective cohort studies. Blood pressure. 2020;29(1):3–12.
18. Zhang D-Y, Guo Q-H, An D-W, Li Y, Wang J-G. A comparative meta-analysis of prospective observational studies on masked hypertension and masked uncontrolled hypertension defined by ambulatory and home blood pressure. Journal of hypertension. 2019 Sep;37(9):1775–85.
19. Pierdomenico SD, Pierdomenico AM, Coccina F, Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic Value of Masked Uncontrolled Hypertension. Hypertension (Dallas, Tex : 1979). 2018;72(4):862–9.

20. Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR. Cardiovascular Events and Mortality in White Coat Hypertension: A Systematic Review and Meta-analysis. Annals of internal medicine. 2019;170(12):853–62.
21. Fujiwara T, Matsumoto C, Asayama K, Ohkubo T, Hoshide S. Are the cardiovascular outcomes of participants with white-coat hypertension poor compared to those of participants with normotension? A systemic review and meta-analysis. Hypertension research : official journal of the Japanese Society of Hypertension. 2019 Jun;42(6):825–33.
22. Ayala Solares JR, Canoy D, Raimondi FED, Zhu Y, Hassaine A, Salimi-Khorshidi G, et al. Long-Term Exposure to Elevated Systolic Blood Pressure in Predicting Incident Cardiovascular Disease: Evidence From Large-Scale Routine Electronic Health Records. Journal of the American Heart Association. 2019 Jun;8(12):e012129.
23. Kirollos S, Skilton M, Patel S, Arnott C. A Systematic Review of Vascular Structure and Function in Pre-eclampsia: Non-invasive Assessment and Mechanistic Links. Frontiers in cardiovascular medicine. 2019;6:166.
24. Salam A, Atkins E, Sundström J, Hirakawa Y, Ettehad D, Emdin C, et al. Effects of blood pressure lowering on cardiovascular events, in the context of regression to the mean: a systematic review of randomized trials. Journal of hypertension. 2019;37(1):16–23.
25. Sakima A, Satonaka H, Nishida N, Yatsu K, Arima H. Optimal blood pressure targets for patients with hypertension: a systematic review and meta-analysis. Hypertension research : official journal of the Japanese Society of Hypertension. 2019 Apr;42(4):483–95.
26. Fei Y, Tsoi M-F, Cheung BMY. Determining the Optimal Systolic Blood Pressure for Hypertensive Patients: A Network Meta-analysis. The Canadian journal of cardiology. 2018;34(12):1581–9.
27. Grenet G, Le HH, Bejan-Angoulvant T, Erpeldinger S, Boussageon R, Kassaï B, et al. Association between difference in blood pressure reduction and risk of cardiovascular events in a type 2 diabetes population: A meta-regression analysis. Diabetes & Metabolism. 2019 Dec;45(6):550–6.

28. Saiz LC, Gorricho J, Garjón J, Celaya MC, Erviti J, Leache L. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. The Cochrane database of systematic reviews. 2018;7:CD010315.
29. Takami Y, Yamamoto K, Arima H, Sakima A. Target blood pressure level for the treatment of elderly hypertensive patients: a systematic review and meta-analysis of randomized trials. Hypertension research : official journal of the Japanese Society of Hypertension. 2019 May;42(5):660–8.
30. Kitagawa K, Yamamoto Y, Arima H, Maeda T, Sunami N, Kanzawa T, et al. Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis. JAMA neurology. 2019 Jul;
31. The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. The Lancet [Internet]. 2010 Jun [cited 2021 Aug 30];375(9733):2215–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673610604849
32. Leon BM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. World Journal of Diabetes. 2015;6(13):1246.
33. Dong J, Ping Y, Wang Y, Zhang Y. The roles of endothelial nitric oxide synthase gene polymorphisms in diabetes mellitus and its associated vascular complications: a systematic review and meta-analysis. Endocrine. 2018;62(2):412–22.
34. Pu Z, Lai L, Yang X, Wang Y, Dong P, Wang D, et al. Acute glycemic variability on admission predicts the prognosis in hospitalized patients with coronary artery disease: a meta-analysis. Endocrine. 2020;67(3):526–34.
35. Liao H-W, Saver J, Yeh H-C, Chen C-HS, Wu Y-L, Lee M, et al. Low fasting glucose and future risks of major adverse outcomes in people without baseline diabetes or cardiovascular disease: a systematic review and meta-analysis. BMJ open. 2019;9(7):e026010.
36. Zhao Y, Guo M, Shi G. Prediabetes predicts adverse cardiovascular outcomes after percutaneous coronary intervention: a meta-analysis. Bioscience reports. 2020;40(1).

37. Pan Y, Chen W, Wang Y. Prediabetes and Outcome of Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-analysis. Journal of Stroke and Cerebrovascular Diseases. 2019 Mar;28(3):683–92.
38. Laichutai N, Defronzo RA. 1456-P: Cardiovascular Outcomes in Subjects with Acute Myocardial Infarction (AMI) and Newly Discovered Abnormal Glucose Tolerance (AGT): A Meta-analysis. Diabetes. 2019 Jun;68(Supplement 1):1456-P.
39. Xun P, Wu Y, He Q, He K. Fasting insulin concentrations and incidence of hypertension, stroke, and coronary heart disease: a meta-analysis of prospective cohort studies. The American Journal of Clinical Nutrition. 2013 Dec 1;98(6):1543–54.
40. Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and Risk of Cardiovascular Disease. Circulation. 1998 Mar 17;97(10):996–1001.
41. Gu T, Yang Q, Ying G, Jin B. Lack of association between insulin resistance as estimated by homeostasis model assessment and stroke risk: A systematic review and meta-analysis. Medical hypotheses. 2020;141:109700.
42. Andrade RLM, Callo G, Horta BL. [C-peptide and cardiovascular mortality: systematic review and meta-analysisPeptido C y mortalidad cardiovascular: revision sistematica y metanalisis]. Peptideo C e mortalidade cardiovascular: revisao sistematica e metanalise. 2019;43:e23.
43. Wang P, Xu Y-Y, Lv T-T, Guan S-Y, Li X-M, Li X-P, et al. Subclinical Atherosclerosis in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Angiology. 2019 Feb 15;70(2):141–59.
44. Lau L, Lew J, Borschmann K, Thijs V, Ekinci EI. Prevalence of diabetes and its effects on stroke outcomes: A meta-analysis and literature review. Journal of Diabetes Investigation. 2019 May 13;10(3):780–92.
45. Mitsios JP, Ekinci EI, Mitsios GP, Churilov L, Thijs V. Relationship Between Glycated Hemoglobin and Stroke Risk: A Systematic Review and Meta-Analysis. Journal of the American Heart Association. 2018 Jun 5;7(11):e007858.
46. Aune D, Schlesinger S, Norat T, Riboli E. Diabetes mellitus and the risk of sudden cardiac death: A systematic review and meta-analysis of prospective studies. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2018;28(6):543–56.

47. Gnatiuc L, Herrington W, Halsey J, Tuomilehto J, Fang X, Kim H, et al. Sex-specific relevance of diabetes to occlusive vascular and other mortality: a collaborative meta-analysis of individual data from 980 793 adults from 68 prospective studies. The Lancet Diabetes & Endocrinology. 2018 Jul;6(7):538–46.
48. Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia. 2014 Aug 25;57(8):1542–51.
49. Wang Y, Nie Y, Yu C. P5496Sex differences in the association between diabetes and risk of cardiovascular disease, cancer, and all-cause and cause-specific mortality: a systematic review and meta-analysis of 5,016,608 participa. European Heart Journal. 2019 Oct 1;40(Supplement_1):3375.
50. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019;62(6):905–14.
51. Li J, Song C, Li C, Liu P, Sun Z, Yang X. Increased risk of cardiovascular disease in women with prior gestational diabetes: A systematic review and meta-analysis. Diabetes Research and Clinical Practice. 2018 Jun;140:324–38.
52. Wang H, Ba Y, Cai R-C, Xing Q. Association between diabetes mellitus and the risk for major cardiovascular outcomes and all-cause mortality in women compared with men: a meta-analysis of prospective cohort studies. BMJ open. 2019;9(7):e024935.
53. Zhang X, Shao F, Zhu L, Ze Y, Zhu D, Bi Y. Cardiovascular and microvascular outcomes of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized controlled cardiovascular outcome trials with trial sequential analysis. BMC Pharmacology and Toxicology. 2018 Dec 17;19(1):58.
54. Dong X-L, Guan F, Xu S-J, Zhu L-X, Zhang P-P, Cheng A-B, et al. Influence of blood glucose level on the prognosis of patients with diabetes mellitus complicated with ischemic stroke. Journal of Research in Medical Sciences. 2018;23(1):10.
55. Pulipati VP, Ravi V, Pulipati P. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus: A systematic review and meta-

analysis. European journal of preventive cardiology. 2020;(101564430):2047487320903638.

56. Pan W, Lu H, Lian B, Liao P, Guo L, Zhang M. Prognostic value of HbA1c for in-hospital and short-term mortality in patients with acute coronary syndrome: a systematic review and meta-analysis. Cardiovascular Diabetology. 2019 Dec 11;18(1):169.
57. Malik AH, Yandrapalli S, Goldberg M, Jain D, Frishman WH, Aronow WS. Cardiovascular Outcomes With the Use of Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes and Chronic Kidney Disease. Cardiology in Review. 2020;28(3):116–24.
58. Zheng SL, Roddick AJ. Applying Network Meta-Analysis to Cardiovascular Outcome Trials of Glucose-Lowering Drugs. JACC: Heart Failure. 2018 Dec;6(12):1052.
59. Fei Y, Tsoi M-F, Kumana CR, Cheung TT, Cheung BMY. Network meta-analysis of cardiovascular outcomes in randomized controlled trials of new antidiabetic drugs. International Journal of Cardiology. 2018 Mar;254:291–6.
60. Bellastella G, Maiorino MI, Longo M, Scappaticcio L, Chiodini P, Esposito K, et al. Glucagon-Like Peptide-1 Receptor Agonists and Prevention of Stroke Systematic Review of Cardiovascular Outcome Trials With Meta-Analysis. Stroke. 2020 Feb;51(2):666–9.
61. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet Diabetes & Endocrinology. 2019 Oct;7(10):776–85.
62. Zhang X, Liu Y, Zhang F, Li J, Tong N. Legacy Effect of Intensive Blood Glucose Control on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Very High Risk or Secondary Prevention of Cardiovascular Disease: A Meta-analysis of Randomized Controlled Trials. Clinical Therapeutics. 2018 May;40(5):776-788.e3.
63. Barer Y, Cohen O, Cukierman-Yaffe T. Effect of glycaemic control on cardiovascular disease in individuals with type 2 diabetes with pre-existing cardiovascular disease: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism [Internet]. 2019 Mar;21(3):732–5. Available from: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1463-1326

64. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practiceThe Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal [Internet]. 2016 Aug 1 [cited 2021 Jul 28];37(29):2315–81. Available from: https://academic.oup.com/eurheartj/article/37/29/2315/1748952

65. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation [Internet]. 2019 Sep 10 [cited 2021 Jul 28];140(11):e596–646. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000678

66. Ma C, Na M, Neumann S, Gao X. Low-Density Lipoprotein Cholesterol and Risk of Hemorrhagic Stroke: a Systematic Review and Dose-Response Meta-analysis of Prospective Studies. Current Atherosclerosis Reports. 2019 Dec 20;21(12):52.

67. Cui Q, Naikoo NA. Modifiable and non-modifiable risk factors in ischemic stroke: a meta-analysis. African health sciences. 2019;19(2):2121–9.

68. Deng Q, Li S, Zhang H, Wang H, Gu Z, Zuo L, et al. Association of serum lipids with clinical outcome in acute ischaemic stroke: A systematic review and meta-analysis. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2019;59:236–44.

69. Ye X, Kong W, Zafar MI, Chen L-L. Serum triglycerides as a risk factor for cardiovascular diseases in type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. Cardiovascular Diabetology. 2019 Dec 15;18(1):48.

70. Collaboration TERF. Lipid-Related Markers and Cardiovascular Disease Prediction. JAMA [Internet]. 2012 Jun 20 [cited 2021 Aug 30];307(23):2499. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.6571

71. Emerging Risk Factors Collaboration;, Sebhat Erqou, Stephen Kaptoge, Philip L Perry, Emanuele Di Angelantonio, Alexander Thompson, et al. Lipoprotein(a) Concentration and

the Risk of Coronary Heart Disease, Stroke, and Nonvascular Mortality. JAMA [Internet]. 2009 Jul 22 [cited 2021 Aug 30];302(4):412. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2009.1063

72. Kouvari M, Panagiotakos DB. The role of lipoprotein (a) in primary and secondary cardiovascular disease prevention: a systematic review of epidemiological studies. Current opinion in cardiology [Internet]. 2019 Jul 1 [cited 2021 Aug 27];34(4):424–34. Available from: https://journals.lww.com/co-cardiology/Fulltext/2019/07000/The_role_of_lipoprotein__a__in_primary_and.18.aspx
73. Sandhu PK, Musaad SMA, Remaley AT, Buehler SS, Strider S, Derzon JH, et al. Lipoprotein Biomarkers and Risk of Cardiovascular Disease: A Laboratory Medicine Best Practices (LMBP) Systematic Review. The Journal of Applied Laboratory Medicine: An AACC Publication [Internet]. 2016 Sep [cited 2021 Aug 27];1(2):214–29. Available from: https://academic.oup.com/jalm/article/1/2/214-229/5587364
74. Zuber V, Gill D, Ala-Korpela M, Langenberg C, Butterworth A, Bottolo L, et al. High-throughput multivariable Mendelian randomization analysis prioritizes apolipoprotein B as key lipid risk factor for coronary artery disease. International Journal of Epidemiology [Internet]. 2021 Jul 9 [cited 2021 Aug 27];50(3):893–901. Available from: https://academic.oup.com/ije/article/50/3/893/5948819
75. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A Meta-Analysis of Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of Cardiovascular Risk. Circulation: Cardiovascular Quality and Outcomes [Internet]. 2011 May [cited 2021 Aug 27];4(3):337–45. Available from: https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.110.959247
76. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: A systematic review and meta-analysis. BMJ Open. 2017 Sep 1;7(9).
77. Akioyamen LE, Tu J V., Genest J, Ko DT, Coutin AJS, Shan SD, et al. Risk of Ischemic Stroke and Peripheral Arterial Disease in Heterozygous Familial Hypercholesterolemia: A Meta-Analysis. Angiology. 2019 Sep 14;70(8):726–36.

78. Anagnostis P, Vaitsi K, Mintziori G, Goulis DG, Mikhailidis DP. Non-coronary atherosclerotic cardiovascular disease in patients with familial hypercholesterolaemia. Current Medical Research and Opinion. 2020 May 3;36(5):731–40.
79. Perrot N, Moschetta D, Boekholdt SM, Valerio V, Martinsson A, Capoulade R, et al. P4667Loss of function in PCSK9, atherogenic lipoprotein concentrations, and calcific aortic valve stenosis. European Heart Journal. 2019 Oct 1;40(Supplement_1):2877.
80. Kouvari M, Panagiotakos DB. The role of lipoprotein (a) in primary and secondary cardiovascular disease prevention. Current Opinion in Cardiology. 2019 Jul;34(4):424–34.
81. Wang S, Ye Q, Pan Y. Serum non-high-density lipoprotein cholesterol is associated with the risk of sudden sensorineural hearing loss. Medicine. 2020 Feb;99(7):e19175.
82. Cao Y, Yan L, Guo N, Yu N, Wang Y, Cao X, et al. Non-high-density lipoprotein cholesterol and risk of cardiovascular disease in the general population and patients with type 2 diabetes: A systematic review and meta-analysis. Diabetes Research and Clinical Practice. 2019 Jan;147:1–8.
83. Michael M, Parisis N, Best M. Nontraditional Lipoprotein Biomarkers: Predictive Power and Risk Stratification*. Journal of Clinical Lipidology. 2019 May;13(3):e2–3.
84. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic Review: Association of Low-Density Lipoprotein Subfractions With Cardiovascular Outcomes. Annals of internal medicine [Internet]. 2009 Apr 7 [cited 2021 Aug 27];150(7):474. Available from: /pmc/articles/PMC6880859/
85. Singh K, Ayers C, Rohatgi A. Differential associations between novel HDL markers and incident atherosclerotic cardiovascular disease by gender and vascular territory: A meta-analysis of large population-based cohorts. Arteriosclerosis, Thrombosis, and Vascular Biology. 2019;39.
86. Wu Y, Fan Z, Tian Y, Liu S, Liu S. Relation between high density lipoprotein particles concentration and cardiovascular events: a meta-analysis. Lipids in Health and Disease. 2018 Dec 19;17(1):142.
87. Jensen MK, Aroner SA, Mukamal KJ, Furtado JD, Post WS, Tsai MY, et al. High-Density Lipoprotein Subspecies Defined by Presence of Apolipoprotein C-III and Incident Coronary Heart Disease in Four Cohorts. Circulation. 2018 Mar 27;137(13):1364–73.

88. Villanueva DLE, Tiongson MD, Ramos JD, Llanes EJ. Monocyte to High-Density Lipoprotein Ratio (MHR) as a predictor of mortality and Major Adverse Cardiovascular Events (MACE) among ST Elevation Myocardial Infarction (STEMI) patients undergoing primary percutaneous coronary intervention: a meta-analysis. Lipids in health and disease. 2020;19(1):55.

89. Ye H, Xu G, Ren L, Peng J. Cholesterol efflux capacity in coronary artery disease. Coronary Artery Disease. 2020 Mar 20;Publish Ah.

90. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease. Journal of the American College of Cardiology. 2013 Jan;61(4):427–36.

91. Schol-Gelok S, Morelli F, Arends LR, Boersma E, Kruip MJHA, Versmissen J, et al. A revised systematic review and meta-analysis on the effect of statins on D-dimer levels. European journal of clinical investigation. 2019 Aug;49(8):e13130.

92. Banach M, Shekoohi N, Mikhailidis D, Lip G, Hernandez A V., Mazidi M. Relationship between low-density lipoprotein cholesterol, lipid lowering agents and the risk of stroke: a meta-analysis of observational studies and randomized controlled trials. Journal of the American College of Cardiology. 2020 Mar;75(11):2080.

93. Dicembrini I, Giannini S, Ragghianti B, Mannucci E, Monami M. Effects of PCSK9 inhibitors on LDL cholesterol, cardiovascular morbidity and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials. Journal of endocrinological investigation. 2019;42(9):1029–39.

94. Masson W, Lobo M, Siniawski D, Molinero G, Masson G, Huerín M, et al. Role of non-statin lipid-lowering therapy in coronary atherosclerosis regression: a meta-analysis and meta-regression. Lipids in Health and Disease. 2020 Dec 27;19(1):111.

95. Navarese EP, Robinson JG, Kowalewski M, Kołodziejczak M, Andreotti F, Bliden K, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering a systematic review and meta-analysis. JAMA - Journal of the American Medical Association. 2018 Apr 17;319(15):1566–79.

96. Shin J, Chung J-W, Jang H-S, Lee J, Hong K-S, Bang OY, et al. Achieved low-density lipoprotein cholesterol level and stroke risk: A meta-analysis of 23 randomised trials. European journal of preventive cardiology. 2019;(101564430):2047487319830503.

97. Cheng Y, Qiao L, Jiang Z, Dong X, Feng H, Gui Q, et al. Significant reduction in the LDL cholesterol increases the risk of intracerebral hemorrhage: a systematic review and meta-analysis of 33 randomized controlled trials. American journal of translational research. 2020;12(2):463–77.
98. Li K, Yao C, Yang X, Di X, Li N, Dong L, et al. Body Mass Index and the Risk of Cardiovascular and All-Cause Mortality Among Patients With Hypertension: A Population-Based Prospective Cohort Study Among Adults in Beijing, China. Journal of Epidemiology. 2016;26(12):654–60.
99. Chen H, Deng Y, Li S. Relation of Body Mass Index Categories with Risk of Sudden Cardiac Death. International Heart Journal. 2019 May 30;60(3):624–30.
100. Aune D, Schlesinger S, Norat T, Riboli E. Body mass index, abdominal fatness, and the risk of sudden cardiac death: a systematic review and dose-response meta-analysis of prospective studies. European journal of epidemiology. 2018;33(8):711–22.
101. Price AJ, Wright FL, Green J, Balkwill A, Kan SW, Yang TO, et al. Differences in risk factors for 3 types of stroke: UK prospective study and meta-analyses. Neurology. 2018;90(4):e298–306.
102. Liu X, Zhang D, Liu Y, Sun X, Hou Y, Wang B, et al. A J-shaped relation of BMI and stroke: Systematic review and dose–response meta-analysis of 4.43 million participants. Nutrition, Metabolism and Cardiovascular Diseases. 2018 Nov;28(11):1092–9.
103. Hong X-Y, Lin J, Gu W-W. Risk factors and therapies in vascular diseases: An umbrella review of updated systematic reviews and meta-analyses. Journal of cellular physiology. 2019;234(6):8221–32.
104. A. J, Shab-Bidar S. AO - Jayedi AO http://orcid. org/0000-0003-4231-3147. Nonlinear dose-response association between body mass index and risk of all-cause and cardiovascular mortality in patients with hypertension: A meta-analysis. Obesity Research and Clinical Practice. 2018;12(1):16–28.
105. Scarale MG, Fontana A, Trischitta V, Copetti M, Menzaghi C. Circulating Adiponectin Levels Are Paradoxically Associated With Mortality Rate: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2019 May 1;104(5):1357–68.

106. Yu F, Li J, Huang Q, Cai H. Increased Peripheral Blood Visfatin Concentrations May Be a Risk Marker of Coronary Artery Disease: A Meta-Analysis of Observational Studies. Angiology. 2018 Oct 29;69(9):825–34.
107. Zhou Z, Macpherson J, Gray SR, Gill JMR, Welsh P, Celis-Morales C, et al. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. Diabetologia [Internet]. 2021 Sep 10 [cited 2021 Aug 30];64(9):1963–72. Available from: https://link.springer.com/10.1007/s00125-021-05484-6
108. Hsueh Y-W, Yeh T-L, Lin C-Y, Tsai S-Y, Liu S-J, Lin C-M, et al. Association of metabolically healthy obesity and elevated risk of coronary artery calcification: a systematic review and meta-analysis. PeerJ. 2020;8(101603425):e8815.
109. Huang M-Y, Wang M-Y, Lin Y-S, Lin C-J, Lo K, Chang I-J, et al. The Association between Metabolically Healthy Obesity, Cardiovascular Disease, and All-Cause Mortality Risk in Asia: A Systematic Review and Meta-Analysis. International Journal of Environmental Research and Public Health. 2020 Feb 19;17(4):1320.
110. Yeh T-L, Chen H-H, Tsai S-Y, Lin C-Y, Liu S-J, Chien K-L. The Relationship between Metabolically Healthy Obesity and the Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2019 Aug 15;8(8):1228.
111. Shab-Bidar S, Djafarian K. 25th European Congress on Obesity, Vienna, Austria, May 23-26, 2018: Abstracts. Obesity Facts. 2018;11(1):1–364.
112. Barzin M, Valizadeh M, Serahati S, Mahdavi M, Azizi F, Hosseinpanah F. Overweight and Obesity: Findings from 20 Years of the Tehran Lipid and Glucose Study. International journal of endocrinology and metabolism. 2018;16(4):e84778.
113. Jayedi A, Rashidy-Pour A, Soltani S, Zargar MS, Emadi A, Shab-Bidar S. Adult weight gain and the risk of cardiovascular disease: a systematic review and dose-response meta-analysis of prospective cohort studies. European journal of clinical nutrition. 2020;
114. Chen Y, Yang X, Wang J, Li Y, Ying D, Yuan H. Weight loss increases all-cause mortality in overweight or obese patients with diabetes. Medicine. 2018 Aug;97(35):e12075.
115. Karahalios A, English DR, Simpson JA. Change in body size and mortality: a systematic review and meta-analysis. International Journal of Epidemiology. 2016 Nov 17;dyw246.

116. Simonsen MK, Hundrup YA, Obel EB, Grønbaek M, Heitmann BL. Intentional weight loss and mortality among initially healthy men and women. Nutrition Reviews. 2008 Jul 8;66(7):375–86.
117. Zomer E, Gurusamy K, Leach R, Trimmer C, Lobstein T, Morris S, et al. Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. Obesity Reviews. 2016 Oct;17(10):1001–11.
118. De Stefani F do C, Pietraroia PS, Fernandes-Silva MM, Faria-Neto J, Baena CP. Observational Evidence for Unintentional Weight Loss in All-Cause Mortality and Major Cardiovascular Events: A Systematic Review and Meta-Analysis. Scientific reports. 2018;8(1):15447.
119. Kane JA, Mehmood T, Munir I, Kamran H, Kariyanna PT, Zhyvotovska A, et al. Cardiovascular Risk Reduction Associated with Pharmacological Weight Loss: A Meta-Analysis. International journal of clinical research & trials. 2019;4(1).
120. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies. International Journal of Cardiology. 2013 Oct;168(5):4761–8.
121. Scarale MG, Fontana A, Trischitta V, Copetti M, Menzaghi C. Circulating Adiponectin Levels Are Paradoxically Associated With Mortality Rate: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2019 May 1;104(5):1357–68.
122. Jayedi A, Shab-Bidar S. Nonlinear dose-response association between body mass index and risk of all-cause and cardiovascular mortality in patients with hypertension: A meta-analysis. Obesity research & clinical practice. 2018;12(1):16–28.
123. Liu X, Zhang D, Liu Y, Sun X, Hou Y, Wang B, et al. A J-shaped relation of BMI and stroke: Systematic review and dose–response meta-analysis of 4.43 million participants. Nutrition, Metabolism and Cardiovascular Diseases. 2018 Nov;28(11):1092–9.
124. Chen H, Deng Y, Li S. Relation of Body Mass Index Categories with Risk of Sudden Cardiac Death. International Heart Journal. 2019 May 30;60(3):624–30.
125. Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, de Gonzalez AB, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. The Lancet. 2016 Aug;388(10046):776–86.

126. Yusuf S, Hawken S, Ôunpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study. The Lancet. 2005 Nov;366(9497):1640–9.
127. Chen Y, Yang X, Wang J, Li Y, Ying D, Yuan H. Weight loss increases all-cause mortality in overweight or obese patients with diabetes. Medicine. 2018 Aug;97(35):e12075.
128. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, et al. BMI and all cause mortality: systematic review and non-linear dose-response meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. BMJ. 2016 May 4;i2156.
129. Kramer CK, Zinman B, Retnakaran R. Are Metabolically Healthy Overweight and Obesity Benign Conditions? Annals of Internal Medicine. 2013 Dec 3;159(11):758.
130. Yu F, Li J, Huang Q, Cai H. Increased Peripheral Blood Visfatin Concentrations May Be a Risk Marker of Coronary Artery Disease: A Meta-Analysis of Observational Studies. Angiology. 2018 Oct 29;69(9):825–34.
131. Lv W-Q, Zhang X, Fan K, Xia X, Zhang Q, Liu H-M, et al. Genetically driven adiposity traits increase the risk of coronary artery disease independent of blood pressure, dyslipidaemia, glycaemic traits. European Journal of Human Genetics. 2018 Oct 11;26(10):1547–53.
132. Chen Q, Li L, Yi J, Huang K, Shen R, Wu R, et al. Waist circumference increases risk of coronary heart disease: Evidence from a Mendelian randomization study. Molecular genetics & genomic medicine. 2020;(101603758):e1186.
133. The Emerging Risk Factors Collaboration. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. The Lancet. 2011 Mar;377(9771):1085–95.
134. Mongraw-Chaffin ML, Peters SAE, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1·2 million participants. The Lancet Diabetes & Endocrinology. 2015 Jun;3(6):437–49.
135. Cao Q, Yu S, Xiong W, Li Y, Li H, Li J, et al. Waist-hip ratio as a predictor of myocardial infarction risk. Medicine. 2018 Jul;97(30):e11639.

136. Huang Y, Xu M, Xie L, Wang T, Huang X, Lv X, et al. Obesity and peripheral arterial disease: A Mendelian Randomization analysis. Atherosclerosis. 2016 Apr;247:218–24.
137. Riaz H, Khan MS, Siddiqi TJ, Usman MS, Shah N, Goyal A, et al. Association Between Obesity and Cardiovascular Outcomes. JAMA Network Open. 2018 Nov 16;1(7):e183788.
138. Kelley GA, Kelley KS, Stauffer BL. Obesity and cardiovascular outcomes: another look at a meta-analysis of Mendelian randomization studies. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2020;68(2):357–63.
139. Darbandi M. Discriminatory Capacity of Anthropometric Indices for Cardiovascular Disease in Adults: A Systematic Review and Meta-Analysis. Preventing Chronic Disease. 2021 Oct 1;17.
140. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nature Reviews Endocrinology 2020 16:3 [Internet]. 2020 Feb 4 [cited 2021 Aug 26];16(3):177–89. Available from: https://www.nature.com/articles/s41574-019-0310-7
141. Blüher M, Laufs U. New concepts for body shape-related cardiovascular risk: role of fat distribution and adipose tissue function. European Heart Journal [Internet]. 2019 Sep 7 [cited 2021 Aug 26];40(34):2856–8. Available from: https://academic.oup.com/eurheartj/article/40/34/2856/5524772
142. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Localization of fat depots and cardiovascular risk. Lipids in Health and Disease [Internet]. 2018 Sep 15 [cited 2021 Aug 26];17(1). Available from: /pmc/articles/PMC6138918/
143. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ (Clinical research ed). 2017 Nov 14;359:j4849.
144. Berger S, Meyre P, Blum S, Aeschbacher S, Ruegg M, Briel M, et al. Bariatric surgery among patients with heart failure: A systematic review and meta-analysis. Open Heart. 2018 Dec 1;5(2):910.

145. Kuno T, Tanimoto E, Morita S, Shimada YJ. Effects of Bariatric Surgery on Cardiovascular Disease: A Concise Update of Recent Advances. Frontiers in Cardiovascular Medicine. 2019 Jul 10;0:94.

146. Wiggins T, Guidozzi N, Welbourn R, Ahmed AR, Markar SR. Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: A systematic review and meta-analysis. PLOS Medicine [Internet]. 2020 Jul 1 [cited 2021 Aug 26];17(7):e1003206. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003206

147. Zhou X, Yu J, Li L, Gloy VL, Nordmann A, Tiboni M, et al. Effects of Bariatric Surgery on Mortality, Cardiovascular Events, and Cancer Outcomes in Obese Patients: Systematic Review and Meta-analysis. Obesity Surgery 2016 26:11 [Internet]. 2016 Mar 18 [cited 2021 Aug 26];26(11):2590–601. Available from: https://link.springer.com/article/10.1007/s11695-016-2144-x

148. Singh P, Subramanian A, Adderley N, Gokhale K, Singhal R, Bellary S, et al. Impact of bariatric surgery on cardiovascular outcomes and mortality: a population-based cohort study. British Journal of Surgery. 2020 Mar 1;107(4):432–42.

149. Kanji S, Wong E, Akioyamen L, Melamed O, Taylor VH. Exploring pre-surgery and post-surgery substance use disorder and alcohol use disorder in bariatric surgery: a qualitative scoping review. International Journal of Obesity. 2019 Sep 18;43(9):1659–74.

150. Beamish AJ, Olbers T, Kelly AS, Inge TH. Cardiovascular effects of bariatric surgery. Nature Reviews Cardiology 2016 13:12 [Internet]. 2016 Oct 20 [cited 2021 Aug 26];13(12):730–43. Available from: https://www.nature.com/articles/nrcardio.2016.162

151. Vilahur G, Badimon JJ, Bugiardini R, Badimon L. Perspectives: The burden of cardiovascular risk factors and coronary heart disease in Europe and worldwide. European Heart Journal, Supplement. 2014 Jan 1;16(SUPPL.A):A7–11.

152. Beaglehole R, Magnus P. The search for new risk factors for coronary heart disease: Occupational therapy for epidemiologists? Vol. 31, International Journal of Epidemiology. Oxford Academic; 2002. p. 1117–22.

153. Lacey B, Herrington WG, Preiss D, Lewington S, Armitage J. The Role of Emerging Risk Factors in Cardiovascular Outcomes. Vol. 19, Current Atherosclerosis Reports. Current Medicine Group LLC 1; 2017.

154. Yong WC, Sanguankeo A, Upala S. Association between sarcoidosis, pulse wave velocity, and other measures of subclinical atherosclerosis: a systematic review and meta-analysis. Clinical rheumatology. 2018 Oct;37(10):2825–32.
155. Buleu F, Sirbu E, Caraba A, Dragan S. Heart Involvement in Inflammatory Rheumatic Diseases: A Systematic Literature Review. Medicina (Kaunas, Lithuania). 2019 Jun;55(6).
156. Erre GL, Buscetta G, Paliogiannis P, Mangoni AA, Carru C, Passiu G, et al. Coronary flow reserve in systemic rheumatic diseases: a systematic review and meta-analysis. Rheumatology international. 2018;38(7):1179–90.
157. Mathieu S, Couderc M, Tournadre A, Soubrier M. Cardiovascular profile in osteoarthritis: a meta-analysis of cardiovascular events and risk factors. Joint bone spine. 2019;86(6):679–84.
158. Tan J, Taskin O, Iews M, Lee AJ, Kan A, Rowe T, et al. Atherosclerotic cardiovascular disease in women with endometriosis: a systematic review of risk factors and prospects for early surveillance. Reproductive biomedicine online. 2019 Dec;39(6):1007–16.
159. Yang S, Zhao LS, Cai C, Shi Q, Wen N, Xu J. Association between periodontitis and peripheral artery disease: a systematic review and meta-analysis. BMC cardiovascular disorders. 2018;18(1):141.
160. Khademi F, Vaez H, Momtazi-Borojeni AA, Majnooni A, Banach M, Sahebkar A. Bacterial infections are associated with cardiovascular disease in Iran: a meta-analysis. Archives of medical science : AMS. 2019 Jul;15(4):902–11.
161. Singh TP, Morris DR, Smith S, Moxon JV, Golledge J. Systematic Review and Meta-Analysis of the Association Between C-Reactive Protein and Major Cardiovascular Events in Patients with Peripheral Artery Disease. European Journal of Vascular and Endovascular Surgery. 2017 Aug;54(2):220–33.
162. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J., et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. The Lancet [Internet]. 2010 Jan [cited 2021 Aug 30];375(9709):132–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673609617177
163. Hsieh WC, Henry BM, Hsieh CC, Maruna P, Omara M, Lindner J. Prognostic Role of Admission C-Reactive Protein Level as a Predictor of In-Hospital Mortality in Type-A

Acute Aortic Dissection: A Meta-Analysis. Vascular and endovascular surgery. 2019 Oct;53(7):547–57.

164. Tian R, Tian M, Wang L, Qian H, Zhang S, Pang H, et al. C-reactive protein for predicting cardiovascular and all-cause mortality in type 2 diabetic patients: A meta-analysis. Cytokine. 2019;117:59–64.
165. Dehghan A, Dupuis J, Barbalic M, Bis JC, Eiriksdottir G, Lu C, et al. Meta-Analysis of Genome-Wide Association Studies in >80 000 Subjects Identifies Multiple Loci for C-Reactive Protein Levels. Circulation. 2011 Feb 22;123(7):731–8.
166. Georgakis MK, Malik R, Björkbacka H, Pana TA, Demissie S, Ayers C, et al. Circulating Monocyte Chemoattractant Protein-1 and Risk of Stroke: Meta-Analysis of Population-Based Studies Involving 17 180 Individuals. Circulation research. 2019;125(8):773–82.
167. Su R. [Biological function of intercellular adhesion molecule-1 gene in coronary heart disease and its mediated primary regulatory network: a literature based secondary analysis]. Zhonghua wei zhong bing ji jiu yi xue. 2019 Apr;31(4):434–8.
168. Song S-Y, Hua C, Dornbors D, Kang R-J, Zhao X-X, Du X, et al. Baseline Red Blood Cell Distribution Width as a Predictor of Stroke Occurrence and Outcome: A Comprehensive Meta-Analysis of 31 Studies. Frontiers in neurology. 2019;10:1237.
169. Zhang S, Diao J, Qi C, Jin J, Li L, Gao X, et al. Predictive value of neutrophil to lymphocyte ratio in patients with acute ST segment elevation myocardial infarction after percutaneous coronary intervention: a meta-analysis. BMC cardiovascular disorders. 2018;18(1):75.
170. Mahlangu T, Dludla P V., Nyambuya TM, Mxinwa V, Mazibuko-Mbeje SE, Cirilli I, et al. A systematic review on the functional role of Th1/Th2 cytokines in type 2 diabetes and related metabolic complications. Cytokine. 2020 Feb;126:154892.
171. Knowles L, Nadeem N, Chowienczyk PJ. Do anti-tumour necrosis factor-α biologics affect subclinical measures of atherosclerosis and arteriosclerosis? A systematic review. British journal of clinical pharmacology. 2020 May;86(5):837–51.
172. Cheng D, Fei Y, Saulnier P-J, Wang N. Circulating TNF receptors and risk of renal disease progression, cardiovascular disease events and mortality in patients with diabetes: a systematic review and meta-analysis. Endocrine. 2020 Apr 7;68(1):32–43.

173. Kolodziej AR, Abo-Aly M, Elsawalhy E, Campbell C, Ziada KM, Abdel-Latif A. Prognostic Role of Elevated Myeloperoxidase in Patients with Acute Coronary Syndrome: A Systemic Review and Meta-Analysis. Mediators of Inflammation. 2019 Jun 25;2019:1–9.
174. Zhou J, Lu Y, Wang S, Chen K. Association between serum amyloid A levels and coronary heart disease: a systematic review and meta-analysis of 26 studies. Inflammation Research. 2020 Apr 22;69(4):331–45.
175. Zhang B, Li X-L, Zhao C-R, Pan C-L, Zhang Z. Interleukin-6 as a Predictor of the Risk of Cardiovascular Disease: A Meta-Analysis of Prospective Epidemiological Studies. Immunological investigations. 2018 Oct;47(7):689–99.
176. IL6R Genetics Consortium Emerging Risk Factors Collaboration, N S, AS B. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. The Lancet. 2012 Mar;379(9822):1205–13.
177. Ursini F, Ruscitti P, Caio GPI, Manfredini R, Giacomelli R, De Giorgio R. The effect of non-TNF-targeted biologics on vascular dysfunction in rheumatoid arthritis: A systematic literature review. Autoimmunity reviews. 2019 May;18(5):501–9.
178. Jones DP, Patel J. Therapeutic approaches targeting inflammation in cardiovascular disorders. Vol. 7, Biology. MDPI AG; 2018.
179. Welsh P, Grassia G, Botha S, Sattar N, Maffia P. Targeting inflammation to reduce cardiovascular disease risk: a realistic clinical prospect? Vol. 174, British Journal of Pharmacology. John Wiley and Sons Inc.; 2017. p. 3898–913.
180. Gao S, Liu J. Association between circulating oxidized low-density lipoprotein and atherosclerotic cardiovascular disease. Chronic Diseases and Translational Medicine. 2017 Jun;3(2):89–94.
181. van den Berg VJ, Vroegindewey MM, Kardys I, Boersma E, Haskard D, Hartley A, et al. Anti-Oxidized LDL Antibodies and Coronary Artery Disease: A Systematic Review. Antioxidants (Basel, Switzerland). 2019 Oct;8(10).
182. Hernández-Ruiz Á, García-Villanova B, Guerra-Hernández E, Amiano P, Ruiz-Canela M, Molina-Montes E. A Review of A Priori Defined Oxidative Balance Scores Relative to Their Components and Impact on Health Outcomes. Nutrients. 2019 Apr;11(4).

183. Zhang W. The Role of NADPH Oxidases in Cardiovascular Disease. Journal of Vascular Medicine & Surgery. 2016;04(03):265.
184. Borghi C, Omboni S, Reggiardo G, Bacchelli S, Esposti DD, Ambrosioni E, et al. Effects of the concomitant administration of xanthine oxidase inhibitors with zofenopril or other ACE-inhibitors in post-myocardial infarction patients: a meta-analysis of individual data of four randomized, double-blind, prospective studies. BMC cardiovascular disorders. 2018;18(1):112.
185. Stehouwer C, Pieters M, Maa MPM de. The Haemostatic System: Coagulation, Platelets, and Fibrinolysis. In: Stanner S, CoeSara S, editors. Cardiovascular Disease Diet, Nutrition and Emerging Risk Factors. 2nd editio. London: Blackwell Publishing; 2018. p. 179–213.
186. Sabater-Lleal M, Huffman JE, de Vries PS, Marten J, Mastrangelo MA, Song C, et al. Genome-Wide Association Transethnic Meta-Analyses Identifies Novel Associations Regulating Coagulation Factor VIII and von Willebrand Factor Plasma Levels. Circulation. 2019;139(5):620–35.
187. Fan Q, Zhu Y, Zhao F. Association of rs2230806 in ABCA1 with coronary artery disease: An updated meta-analysis based on 43 research studies. Medicine. 2020;99(4):e18662.
188. Willeit P, Thompson A, Aspelund T, Rumley A, Eiriksdottir G, Lowe G, et al. Hemostatic Factors and Risk of Coronary Heart Disease in General Populations: New Prospective Study and Updated Meta-Analyses. Stoll M, editor. PLoS ONE. 2013 Feb 7;8(2):e55175.
189. Emerging Risk Factors Collaboration. C-Reactive Protein, Fibrinogen, and Cardiovascular Disease Prediction. New England Journal of Medicine. 2012 Oct 4;367(14):1310–20.
190. Sabater-Lleal M, Huang J, Chasman D, Naitza S, Dehghan A, Johnson AD, et al. Multiethnic Meta-Analysis of Genome-Wide Association Studies in >100 000 Subjects Identifies 23 Fibrinogen-Associated Loci but No Strong Evidence of a Causal Association Between Circulating Fibrinogen and Cardiovascular Disease. Circulation. 2013 Sep 17;128(12):1310–24.
191. Ye Z, Liu EH, Higgins JP, Keavney BD, Lowe G DO, Collins R, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66 155 cases and 91 307 controls. The Lancet. 2006 Feb;367(9511):651–8.

192. Mai V, Guay C-A, Perreault L, Bonnet S, Bertoletti L, Lacasse Y, et al. Extended Anticoagulation for VTE: A Systematic Review and Meta-Analysis. Chest. 2019;155(6):1199–216.

193. Lucore CL, Sobel BE. Interactions of tissue-type plasminogen activator with plasma inhibitors and their pharmacologic implications. Circulation [Internet]. 1988 Mar [cited 2021 Aug 26];77(3):660–9. Available from: https://www.ahajournals.org/doi/10.1161/01.CIR.77.3.660

194. Song C, Burgess S, Eicher JD, O'Donnell CJ, Johnson AD, Huang J, et al. Causal Effect of Plasminogen Activator Inhibitor Type 1 on Coronary Heart Disease. Journal of the American Heart Association [Internet]. 2017 Nov 6 [cited 2021 Aug 26];6(6). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.116.004918

195. Jung RG, Motazedian P, Ramirez FD, Simard T, di Santo P, Visintini S, et al. Association between plasminogen activator inhibitor-1 and cardiovascular events: a systematic review and meta-analysis. Thrombosis Journal 2018 16:1 [Internet]. 2018 Jun 5 [cited 2021 Aug 26];16(1):1–12. Available from: https://thrombosisjournal.biomedcentral.com/articles/10.1186/s12959-018-0166-4

196. Song C, Burgess S, Eicher JD, O'Donnell CJ, Johnson AD, Huang J, et al. Causal Effect of Plasminogen Activator Inhibitor Type 1 on Coronary Heart Disease. Journal of the American Heart Association [Internet]. 2017 Nov 6 [cited 2021 Aug 27];6(6). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.116.004918

197. Bruins Slot KM, Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. The Cochrane database of systematic reviews. 2018;3:CD008980.

198. Escobar C, Martí-Almor J, Pérez Cabeza A, Martínez-Zapata MJ. Direct Oral Anticoagulants Versus Vitamin K Antagonists in Real-life Patients With Atrial Fibrillation. A Systematic Review and Meta-analysis. Revista espanola de cardiologia (English ed). 2019 Apr;72(4):305–16.

199. Meinel TR, Frey S, Arnold M, Kendroud S, Fischer U, Kaesmacher J, et al. Clinical presentation, diagnostic findings and management of cerebral ischemic events in patients on treatment with non-vitamin K antagonist oral anticoagulants - A systematic review. PloS one. 2019;14(3):e0213379.

200. Caldeira D, David C, Costa J, Ferreira JJ, Pinto FJ. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease: systematic review and meta-analysis. European heart journal Cardiovascular pharmacotherapy. 2018;4(2):111–8.

201. Gupta S, Um KJ, Pandey A, McIntyre WF, Ivanova M, Allahverdi Y, et al. Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients Undergoing Cardioversion for Atrial Fibrillation: a Systematic Review and Meta-analysis. Cardiovascular drugs and therapy. 2019;33(3):339–52.

202. Liu M, Lu W, Chen L, Wang Y, Zhao Z, Zhang M, et al. An up-dated meta-analysis of major adverse cardiac events on triple versus dual antiplatelet therapy after percutaneous coronary intervention in patients with type 2 diabetes mellitus. Data in brief. 2018;20(101654995):448–53.

203. Loader J, Khouri C, Taylor F, Stewart S, Lorenzen C, Cracowski J-L, et al. The continuums of impairment in vascular reactivity across the spectrum of cardiometabolic health: A systematic review and network meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2019;20(6):906–20.

204. Zhou Y-Y, Zhou X-D, Wu S-J, Fan D-H, Van Poucke S, Chen Y-P, et al. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: A systematic review and meta-analysis. Hepatology communications. 2018;2(4):376–92.

205. Georgakis MK, Chatzopoulou D, Tsivgoulis G, Petridou ET. Albuminuria and Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society. 2018;66(3):509–17.

206. Thijssen DHJ, Bruno RM, van Mil ACCM, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. European Heart Journal [Internet]. 2019 Aug 7 [cited 2021 Aug 26];40(30):2534–47. Available from: https://academic.oup.com/eurheartj/article/40/30/2534/5519997

207. Tousoulis D, Antoniades C, Stefanadis C. Evaluating endothelial function in humans: a guide to invasive and non-invasive techniques. Heart [Internet]. 2005 Apr [cited 2021 Aug 26];91(4):553. Available from: /pmc/articles/PMC1768833/

208. Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: A systematic review with meta-analysis. International Journal of Cardiology [Internet]. 2013 Sep 20 [cited 2021 Aug 26];168(1):344–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167527312011539

209. Matsuzawa Y, Kwon T, Lennon RJ, Lerman LO, Lerman A. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. Journal of the American Heart Association [Internet]. 2015 Oct 29 [cited 2021 Aug 26];4(11). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.115.002270

210. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. The International Journal of Cardiovascular Imaging [Internet]. 2010 Aug 26 [cited 2021 Aug 26];26(6):631–40. Available from: http://link.springer.com/10.1007/s10554-010-9616-1

211. Xu Y, Arora RC, Hiebert BM, Lerner B, Szwajcer A, McDonald K, et al. Non-invasive endothelial function testing and the risk of adverse outcomes: a systematic review and meta-analysis. European Heart Journal - Cardiovascular Imaging [Internet]. 2014 Jul [cited 2021 Aug 26];15(7):736–46. Available from: https://academic.oup.com/ehjcimaging/article-lookup/doi/10.1093/ehjci/jet256

212. Griessenauer CJ, Farrell S, Sarkar A, Zand R, Abedi V, Holland N, et al. Genetic susceptibility to cerebrovascular disease: A systematic review. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2018;38(11):1853–71.

213. Xu B, Zhan R, Mai H, Wu Z, Zhu P, Liang Y, et al. The association between vascular endothelial growth factor gene polymorphisms and stroke: A PRISMA-compliant meta-analysis. Medicine. 2019 Mar;98(11):e14696.

214. Wang L, Ge H, Peng L, Wang B. A meta-analysis of the relationship between VEGFR2 polymorphisms and atherosclerotic cardiovascular diseases. Clinical cardiology. 2019 Oct;42(10):860–5.

215. Li Y, Wang S, Zhang D, Xu X, Yu B, Zhang Y. The association of functional polymorphisms in genes expressed in endothelial cells and smooth muscle cells with the myocardial infarction. Human Genomics. 2019 Dec 24;13(1):5.

216. Nepal G, Ojha R, Dulal HP, Yadav BK. Association between Lys198Asn polymorphism of endothelin-1 gene and ischemic stroke: A meta-analysis. Brain and behavior. 2019;9(10):e01424.

217. Ma W-Q, Wang Y, Han X-Q, Zhu Y, Liu N-F. Association of genetic polymorphisms in vascular endothelial growth factor with susceptibility to coronary artery disease: a meta-analysis. BMC medical genetics. 2018;19(1):108.

218. Ali H. SCUBE2, vascular endothelium, and vascular complications: A systematic review. Biomedicine & Pharmacotherapy. 2020 Jul;127:110129.

219. Totzeck M, Mincu R-I, Mrotzek S, Schadendorf D, Rassaf T. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: A meta-analysis of approximately 29,000 cancer patients. European journal of preventive cardiology. 2018;25(5):482–94.

220. Groot E de, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart J-C, et al. Measurement of Arterial Wall Thickness as a Surrogate Marker for Atherosclerosis. Circulation [Internet]. 2004 Jun 15 [cited 2021 Aug 26];109(23 SUPPL.). Available from: https://www.ahajournals.org/doi/abs/10.1161/01.cir.0000131516.65699.ba

221. Katakami N, Kaneto H, Shimomura I. Carotid ultrasonography: A potent tool for better clinical practice in diagnosis of atherosclerosis in diabetic patients. Journal of Diabetes Investigation [Internet]. 2014 Jan [cited 2021 Aug 26];5(1):3. Available from: /pmc/articles/PMC4025224/

222. Sabeti S, Schlager O, Exner M, Mlekusch W, Amighi J, Dick P, et al. Progression of Carotid Stenosis Detected by Duplex Ultrasonography Predicts Adverse Outcomes in Cardiovascular High-Risk Patients. Stroke [Internet]. 2007 Nov [cited 2021 Aug 26];38(11):2887–94. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.107.488387

223. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of Clinical Cardiovascular Events With Carotid Intima-Media Thickness. Circulation [Internet]. 2007 Jan 30 [cited 2021 Aug 26];115(4):459–67. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.628875

224. Barker DJP, Fall CHD. Fetal and infant origins of cardiovascular disease. Archives of Disease in Childhood. 1993;68(6):797–9.

225. Pullar J, Wickramasinghe K, Demaio AR, Roberts N, Perez-Blanco K-M, Noonan K, et al. The impact of maternal nutrition on offspring's risk of non-communicable diseases in adulthood: a systematic review. Journal of global health. 2019;9(2):20405.
226. Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero : systematic review and meta-analysis. Journal of Developmental Origins of Health and Disease. 2020 Dec 6;11(6):599–616.
227. Wang J, Moore D, Subramanian A, Cheng KK, Toulis KA, Qiu X, et al. Gestational dyslipidaemia and adverse birthweight outcomes: a systematic review and meta-analysis. Obesity Reviews. 2018 Sep;19(9):1256–68.
228. Andraweera PH, Lassi ZS. Cardiovascular Risk Factors in Offspring of Preeclamptic Pregnancies-Systematic Review and Meta-Analysis. The Journal of pediatrics. 2019;208:104-113.e6.
229. Gunning MN, Sir Petermann T, Crisosto N, van Rijn BB, de Wilde MA, Christ JP, et al. Cardiometabolic health in offspring of women with PCOS compared to healthy controls: a systematic review and individual participant data meta-analysis. Human Reproduction Update. 2020 Jan 1;26(1):104–18.
230. Markopoulou P, Papanikolaou E, Analytis A, Zoumakis E, Siahanidou T. Preterm Birth as a Risk Factor for Metabolic Syndrome and Cardiovascular Disease in Adult Life: A Systematic Review and Meta-Analysis. The Journal of Pediatrics. 2019 Jul;210:69-80.e5.
231. Knop MR, Geng T-T, Gorny AW, Ding R, Li C, Ley SH, et al. Birth Weight and Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension in Adults: A Meta-Analysis of 7 646 267 Participants From 135 Studies. Journal of the American Heart Association. 2018 Dec 4;7(23):e008870.
232. Menendez-Castro C, Rascher W, Hartner A. Intrauterine growth restriction - impact on cardiovascular diseases later in life. Molecular and Cellular Pediatrics. 2018 Dec 20;5(1):4.
233. Kolding L, Eken H, Uldbjerg N. Drug exposure during pregnancy and fetal cardiac function – a systematic review. Journal of Perinatal Medicine. 2020 Mar 26;48(3):199–208.

234. Mintjens S, Menting MD, Daams JG, van Poppel MNM, Roseboom TJ, Gemke RJBJ. Cardiorespiratory Fitness in Childhood and Adolescence Affects Future Cardiovascular Risk Factors: A Systematic Review of Longitudinal Studies. Sports medicine (Auckland, NZ). 2018 Nov;48(11):2577–605.

235. Knop MR, Geng T, Gorny AW, Ding R, Li C, Ley SH, et al. Birth Weight and Risk of Type 2 Diabetes Mellitus, Cardiovascular Disease, and Hypertension in Adults: A Meta-Analysis of 7 646 267 Participants From 135 Studies. Journal of the American Heart Association. 2018 Dec 4;7(23):e008870.

236. Pathirana MM, Lassi ZS, Roberts CT, Andraweera PH. Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus in utero : systematic review and meta-analysis. Journal of Developmental Origins of Health and Disease. 2020 Dec 6;11(6):599–616.

237. Stewart CP, Christian P, Schulze KJ, LeClerq SC, West KP, Khatry SK. Antenatal Micronutrient Supplementation Reduces Metabolic Syndrome in 6- to 8-Year-Old Children in Rural Nepal. The Journal of Nutrition [Internet]. 2009 Aug 1 [cited 2021 Aug 30];139(8):1575–81. Available from: https://academic.oup.com/jn/article/139/8/1575/4670514

238. Devakumar D, Chaube SS, Wells JCK, Saville NM, Ayres JG, Manandhar DS, et al. Effect of antenatal multiple micronutrient supplementation on anthropometry and blood pressure in mid-childhood in Nepal: follow-up of a double-blind randomised controlled trial. The Lancet Global Health [Internet]. 2014 Nov [cited 2021 Aug 30];2(11):e654–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2214109X14703146

239. Varbo A, Benn M, Smith GD, Timpson NJ, Tybjærg-Hansen A, Nordestgaard BG. Remnant Cholesterol, Low-Density Lipoprotein Cholesterol, and Blood Pressure as Mediators From Obesity to Ischemic Heart Disease. Circulation Research. 2015 Feb 13;116(4):665–73.

240. Xu L, Borges MC, Hemani G, Lawlor DA. The role of glycaemic and lipid risk factors in mediating the effect of BMI on coronary heart disease: a two-step, two-sample Mendelian randomisation study. Diabetologia. 2017 Nov 9;60(11):2210–20.

241. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. Vol. 444, Nature. Nature Publishing Group; 2006. p. 875–80.

242. Cercato C, Fonseca FA. Cardiovascular risk and obesity. Vol. 11, Diabetology and Metabolic Syndrome. BioMed Central Ltd.; 2019. p. 74.
243. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: Where do we stand? Vol. 15, Vascular Health and Risk Management. Dove Medical Press Ltd.; 2019. p. 89–100.
244. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. Nerurkar P V., editor. PLOS ONE. 2018 Mar 20;13(3):e0194127.
245. Goodarzi MO, Rotter JI. Genetics Insights in the Relationship Between Type 2 Diabetes and Coronary Heart Disease. Circulation Research. 2020 May 22;126(11):1526–48.
246. Bhatnagar A. Environmental Determinants of Cardiovascular Disease. Vol. 121, Circulation Research. Lippincott Williams and Wilkins; 2017. p. 162–80.
247. Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. Nature Reviews Cardiology. Nature Research; 2020. p. 1–17.
248. Tzoulaki I, Elliott P, Kontis V, Ezzati M. Worldwide Exposures to Cardiovascular Risk Factors and Associated Health Effects. Circulation. 2016 Jun 7;133(23):2314–33.
249. Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: A systematic review and meta-analysis. Vol. 102, American Journal of Clinical Nutrition. American Society for Nutrition; 2015. p. 276–94.
250. Zhong VW, Van Horn L, Cornelis MC, Wilkins JT, Ning H, Carnethon MR, et al. Associations of Dietary Cholesterol or Egg Consumption with Incident Cardiovascular Disease and Mortality. JAMA - Journal of the American Medical Association. 2019 Mar 19;321(11):1081–95.
251. World Health Organization: Regional Office for Europe. Eliminating trans fats in Europe A policy brief. Copenhagen; 2015.
252. Bang HO, Dyerberg J. Lipid Metabolism and Ischemic Heart Disease in Greenland Eskimos. Advances in Nutritional Research [Internet]. 1980 [cited 2021 Aug 26];1–22. Available from: https://link.springer.com/chapter/10.1007/978-1-4757-4448-4_1
253. Chen G-C, Yang J, Eggersdorfer M, Zhang W, Qin L-Q. N-3 long-chain polyunsaturated fatty acids and risk of all-cause mortality among general populations: a meta-analysis.

Scientific Reports [Internet]. 2016 Sep 16 [cited 2021 Aug 26];6(1):28165. Available from: http://www.nature.com/articles/srep28165

254. Roos B de, Mavrommatis Y, Brouwer IA. Long-chain n-3 polyunsaturated fatty acids: new insights into mechanisms relating to inflammation and coronary heart disease. British Journal of Pharmacology [Internet]. 2009 Sep [cited 2021 Aug 26];158(2):413. Available from: /pmc/articles/PMC2757681/

255. Hooper L, Summerbell CD, Thompson R, Sills D, Roberts FG, Moore H, et al. Reduced or modified dietary fat for preventing cardiovascular disease. In: Hooper L, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2011 [cited 2021 Aug 26]. Available from: https://doi.wiley.com/10.1002/14651858.CD002137.pub2

256. Kones R, Howell S, Rumana U. n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease: Principles, Practices, Pitfalls, and Promises - A Contemporary Review. Medical Principles and Practice [Internet]. 2017 Feb 1 [cited 2021 Aug 26];26(6):497–508. Available from: https://www.karger.com/Article/FullText/485837

257. Ho FK, Gray SR, Welsh P, Petermann-Rocha F, Foster H, Waddell H, et al. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants.

258. Noto H, Goto A, Tsujimoto T, Noda M. Low-Carbohydrate Diets and All-Cause Mortality: A Systematic Review and Meta-Analysis of Observational Studies. Vol. 8, PLoS ONE. Public Library of Science; 2013.

259. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. The Lancet. 2019 Feb 2;393(10170):434–45.

260. Threapleton DE, Greenwood DC, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ. 2013 Dec 19;347(dec19 2):f6879–f6879.

261. Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. JAMA Cardiology. 2019 Aug 1;4(8):765–75.

262. Jenkins DJA, Spence JD, Giovannucci EL, Kim Y in, Josse R, Vieth R, et al. Supplemental Vitamins and Minerals for CVD Prevention and Treatment. Vol. 71, Journal of the American College of Cardiology. Elsevier USA; 2018. p. 2570–84.
263. Wang T, Xu L. Circulating vitamin E levels and risk of coronary artery disease and myocardial infarction: A mendelian randomization study. Nutrients. 2019 Sep 1;11(9).
264. Xi B, Huang Y, Reilly KH, Li S, Zheng R, Barrio-Lopez MT, et al. Sugar-sweetened beverages and risk of hypertension and CVD: A dose-response meta-analysis. Vol. 113, British Journal of Nutrition. Cambridge University Press; 2015. p. 709–17.
265. Chen Z, Glisic M, Song M, Aliahmad HA, Zhang X, Moumdjian AC, et al. Dietary protein intake and all-cause and cause-specific mortality: results from the Rotterdam Study and a meta-analysis of prospective cohort studies. European Journal of Epidemiology. 2020 May 1;35(5):411–29.
266. Fontecha J, Calvo MV, Juarez M, Gil A, Martínez-Vizcaino V. Milk and Dairy Product Consumption and Cardiovascular Diseases: An Overview of Systematic Reviews and Meta-Analyses. Advances in nutrition (Bethesda, Md). 2019;10:S164–89.
267. Pagliai G, Dinu M, Madarena MP, Bonaccio M, Iacoviello L, Sofi F. Consumption of ultra-processed foods and health status: a systematic review and meta-analysis. British Journal of Nutrition. 2020 Aug 14;1–11.
268. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Current Opinion in Lipidology. 2002 Feb;13(1):3–9.
269. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: An umbrella review of meta-analyses of observational studies and randomised trials. Vol. 72, European Journal of Clinical Nutrition. Nature Publishing Group; 2018. p. 30–43.
270. Bhat S, Mocciaro G, Ray S. The association of dietary patterns and carotid intima-media thickness: A synthesis of current evidence. Nutrition, Metabolism and Cardiovascular Diseases. 2019 Dec;29(12):1273–87.
271. Schwingshackl L, Chaimani A, Schwedhelm C, Toledo E, Pünsch M, Hoffmann G, et al. Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis. Vol. 59, Critical Reviews in Food Science and Nutrition. Taylor and Francis Inc.; 2019. p. 2674–87.

272. Matsuyama S, Sawada N, Tomata Y, Zhang S, Goto A, Yamaji T, et al. Association between adherence to the Japanese diet and all-cause and cause-specific mortality: the Japan Public Health Center-based Prospective Study. European Journal of Nutrition 2020 60:3 [Internet]. 2020 Jul 16 [cited 2021 Aug 30];60(3):1327–36. Available from: https://link.springer.com/article/10.1007/s00394-020-02330-0

273. Ghaedi E, Mohammadi M, Mohammadi H, Ramezani-Jolfaie N, Malekzadeh J, Hosseinzadeh M, et al. Effects of a Paleolithic Diet on Cardiovascular Disease Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Advances in nutrition (Bethesda, Md). 2019;10(4):634–46.

274. Ramezani-Jolfaie N, Mohammadi M, Salehi-Abargouei A. The effect of healthy Nordic diet on cardio-metabolic markers: a systematic review and meta-analysis of randomized controlled clinical trials. European journal of nutrition. 2019 Sep;58(6):2159–74.

275. Noto H, Goto A, Tsujimoto T, Noda M. Low-Carbohydrate Diets and All-Cause Mortality: A Systematic Review and Meta-Analysis of Observational Studies. Vol. 8, PLoS ONE. Public Library of Science; 2013.

276. Goldenberg JZ, Day A, Brinkworth GD, Sato J, Yamada S, Jönsson T, et al. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data. BMJ [Internet]. 2021 Jan 13 [cited 2021 Aug 30];372:m4743. Available from: https://www.bmj.com/content/372/bmj.m4743

277. Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, et al. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. The Lancet Public Health. 2018 Sep 1;3(9):e419–28.

278. Hernán MA, Robins JM. Causal Inference: What If. 2019;

279. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. International Journal of Obesity 2008 32:3 [Internet]. 2008 Aug 11 [cited 2021 Aug 26];32(3):S8–14. Available from: https://www.nature.com/articles/ijo200882

280. Splawa-Neyman J. On the application of probability theory to agricultural experiments. Essay on principles. Section 9. Statistical Science. 1990;5(4):465–72.

281. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. Journal of Educational Psychology. 1974;66(5):688–701.
282. Pearl J. Causality: Models, reasoning, and inference, second edition. Causality: Models, Reasoning, and Inference, Second Edition. Cambridge University Press; 2011. 1–464.
283. Imbens G. Nonparametric Estimation of Average Treatment Effects under Exogeneity: A Review. Cambridge, MA; 2003 Oct.
284. Hernán MA, Hsu J, Healy B. A Second Chance to Get Causal Inference Right: A Classification of Data Science Tasks. https://doi.org/101080/0933248020191579578 [Internet]. 2019 Jan 2 [cited 2021 Aug 26];32(1):42–9. Available from: https://www.tandfonline.com/doi/abs/10.1080/09332480.2019.1579578
285. Glass TA, Goodman SN, Hernán MA, Samet JM. Causal Inference in Public Health. http://dx.doi.org/101146/annurev-publhealth-031811-124606 [Internet]. 2013 Mar 20 [cited 2021 Aug 26];34:61–75. Available from: https://www.annualreviews.org/doi/abs/10.1146/annurev-publhealth-031811-124606
286. Palmnäs M, Brunius C, Shi L, Rostgaard-Hansen A, Torres NE, González-Domínguez R, et al. Perspective: Metabotyping—A Potential Personalized Nutrition Strategy for Precision Prevention of Cardiometabolic Disease. Advances in Nutrition [Internet]. 2020 May 1 [cited 2021 Aug 30];11(3):524–32. Available from: https://academic.oup.com/advances/article/11/3/524/5645624
287. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized Nutrition by Prediction of Glycemic Responses. Cell. 2015 Nov 19;163(5):1079–94.
288. Gibney ER. Personalised nutrition - phenotypic and genetic variation in response to dietary intervention. Proceedings of the Nutrition Society. 2020 May 1;79(2):236–45.
289. Macaninch E, Buckner L, Amin P, Broadley I, Crocombe D, Herath D, et al. Time for nutrition in medical education. BMJ Nutrition, Prevention & Health. 2020 Jun 1;3(1):40–8.

Figure legends

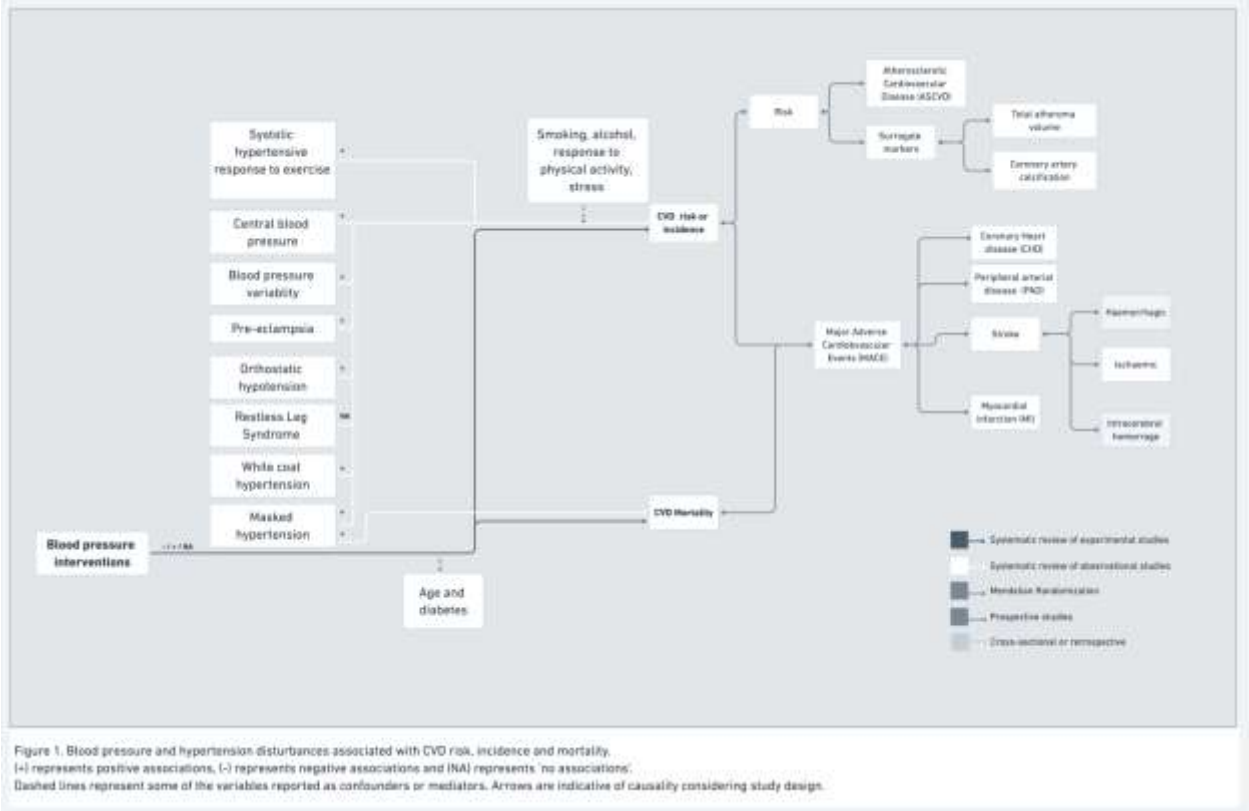

Figure 1. Blood pressure and hypertension disturbances associated with CVD risk, incidence and mortality.
(+) represents positive associations, (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

Figure 1. Hypertension and blood pressure disturbances associated with CVD risk, incidence and mortality.

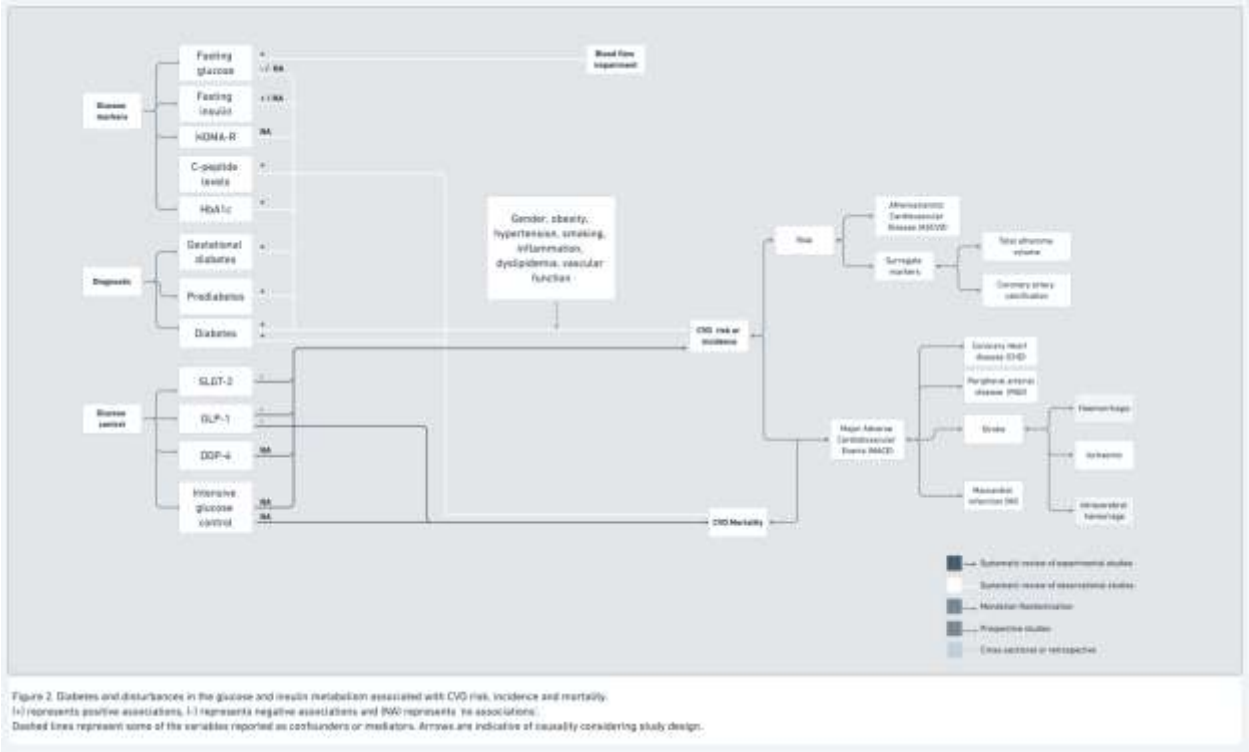

Figure 2. Diabetes and disturbances in the glucose and insulin metabolism associated with CVD risk, incidence and mortality.

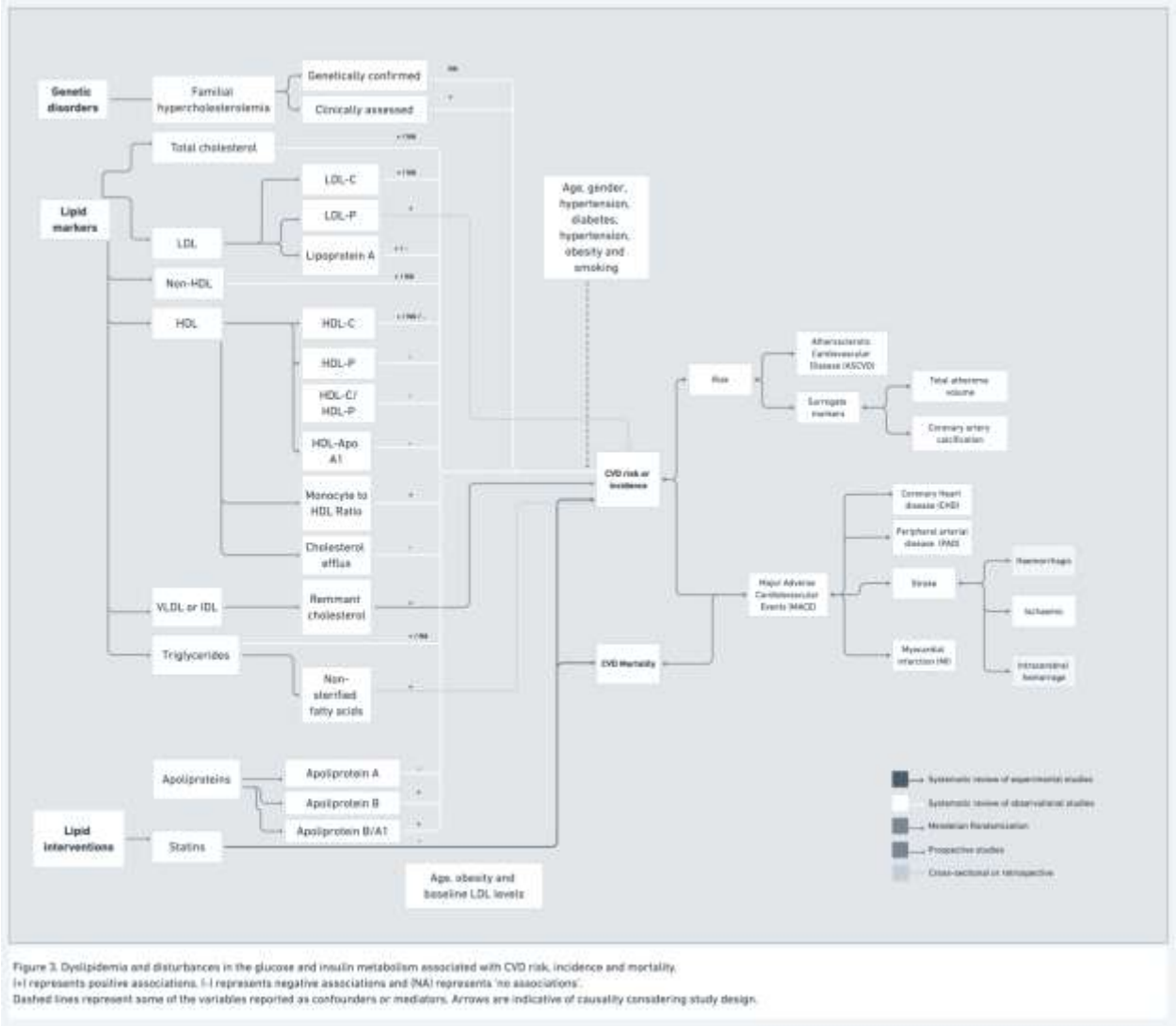

Figure 3. Dyslipidemia and disturbances in the glucose and insulin metabolism associated with CVD risk, incidence and mortality.
(+) represents positive associations. (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

Figure 3. Dyslipidemia and lipid disorders associated with CVD risk, incidence and mortality.

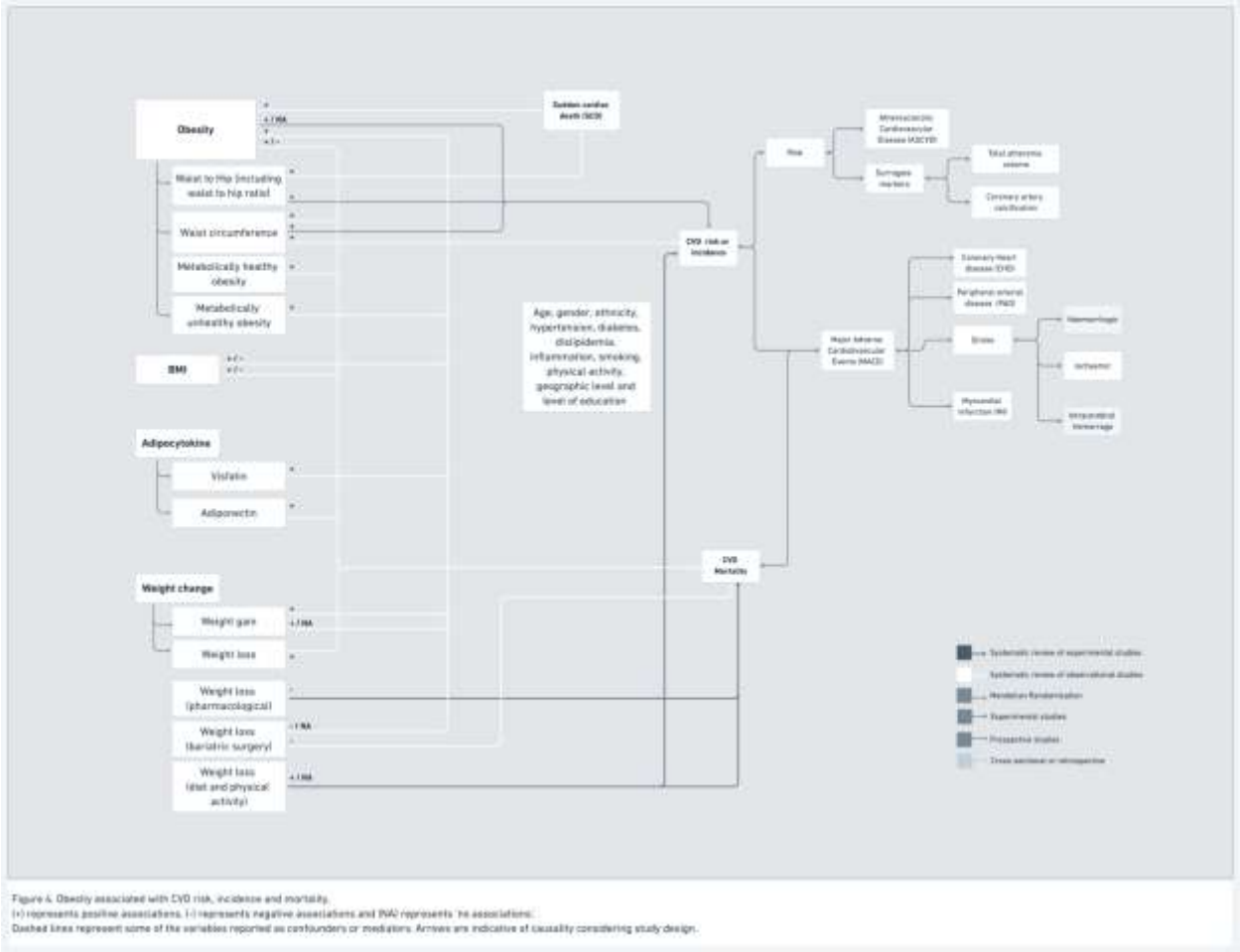

Figure 4. Obesity associated with CVD risk, incidence and mortality.

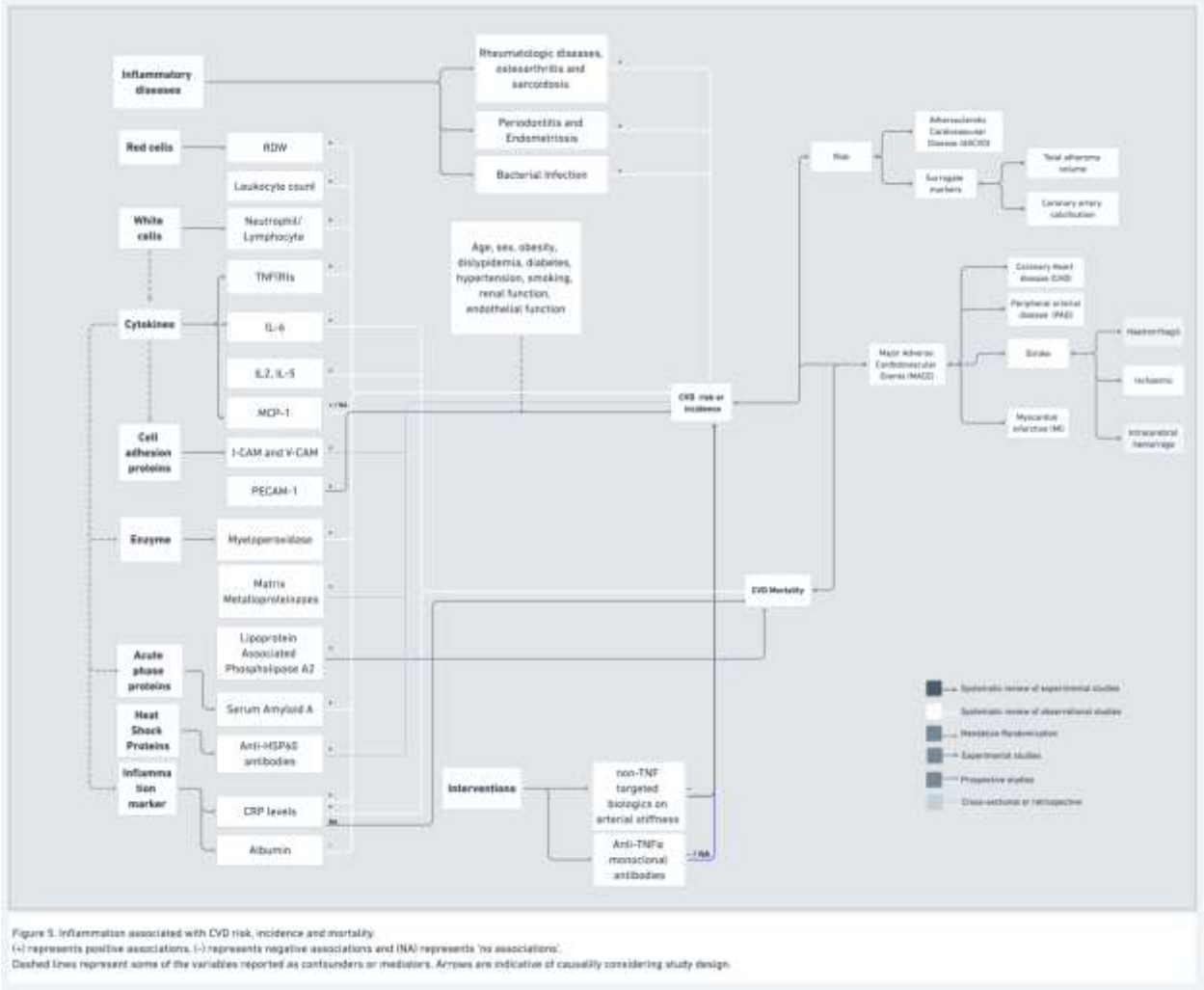

Figure 5. Inflammation associated with CVD risk, incidence and mortality.

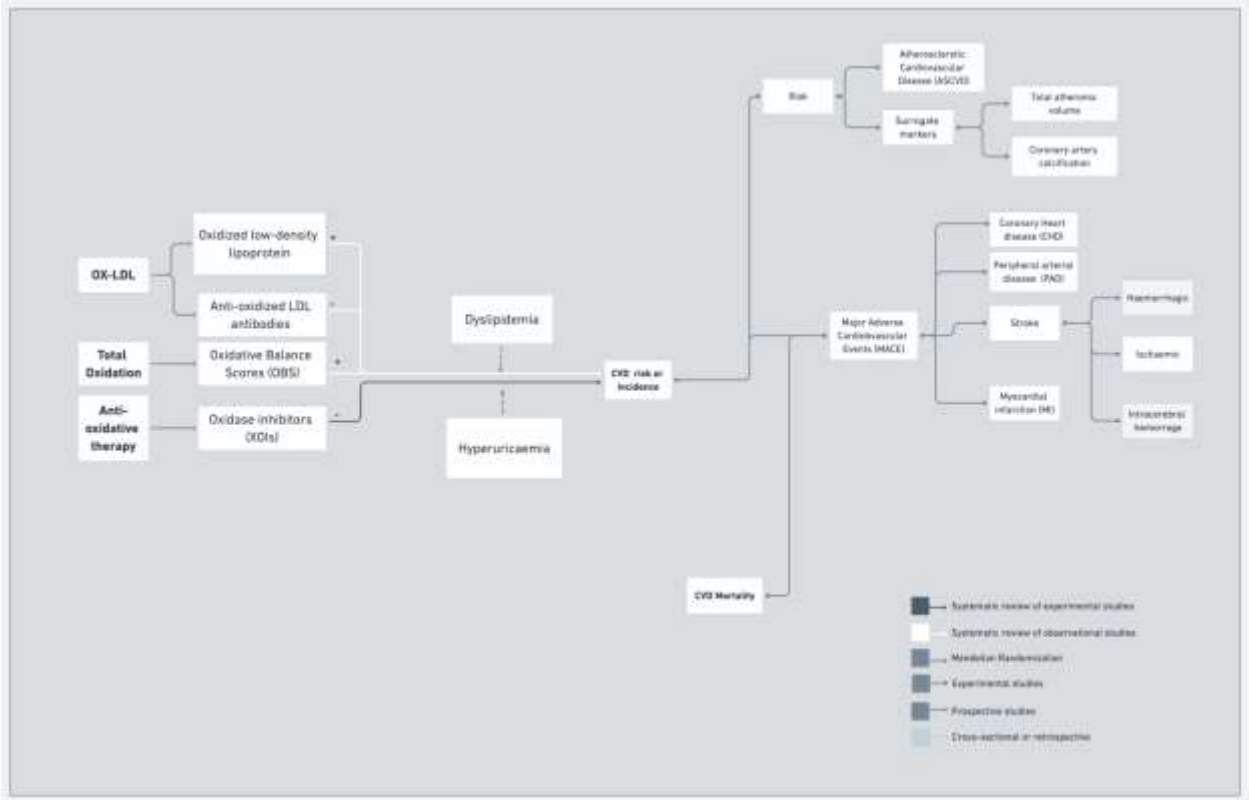

Figure 6. Oxidative stress associated with CVD risk, incidence and mortality.
(+) represents positive associations, (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

Figure 6. Oxidative stress associated with CVD risk, incidence and mortality.

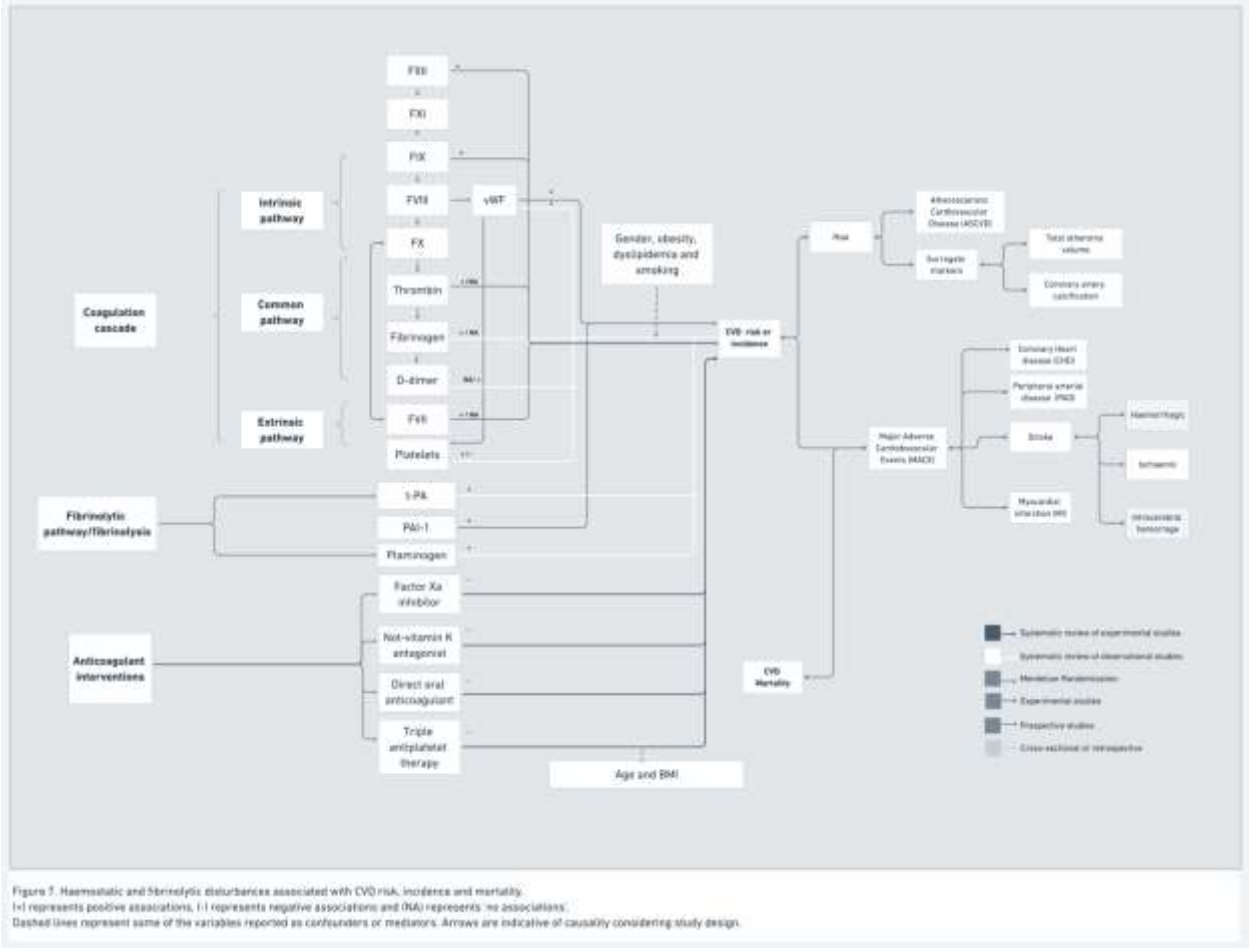

Figure 7. Haemostatic and fybrinolitc disturbances associated with CVD risk, incidence and mortality.

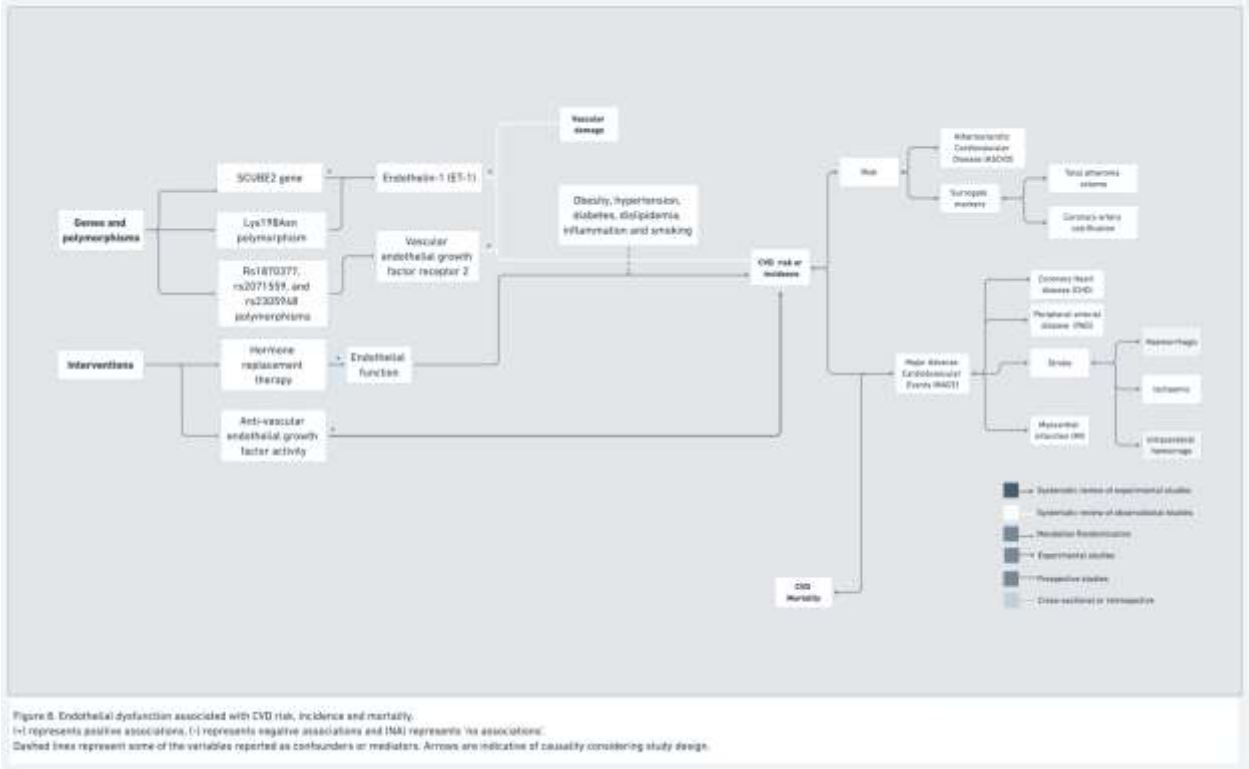

Figure 8. Endothelial dysfunction associated with CVD risk, incidence and mortality.
(+) represents positive associations, (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

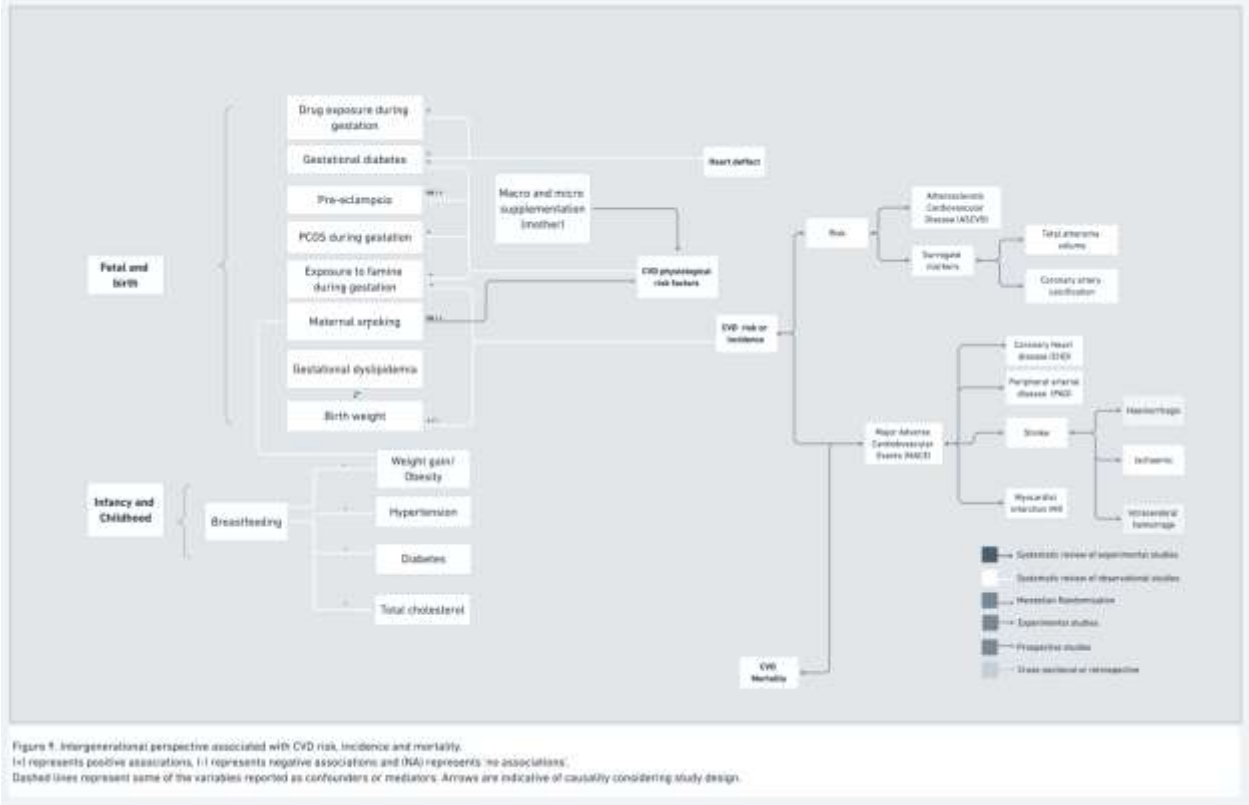

Figure 9. Intergeenrational perspective associated with CVD risk, incidence and mortality.

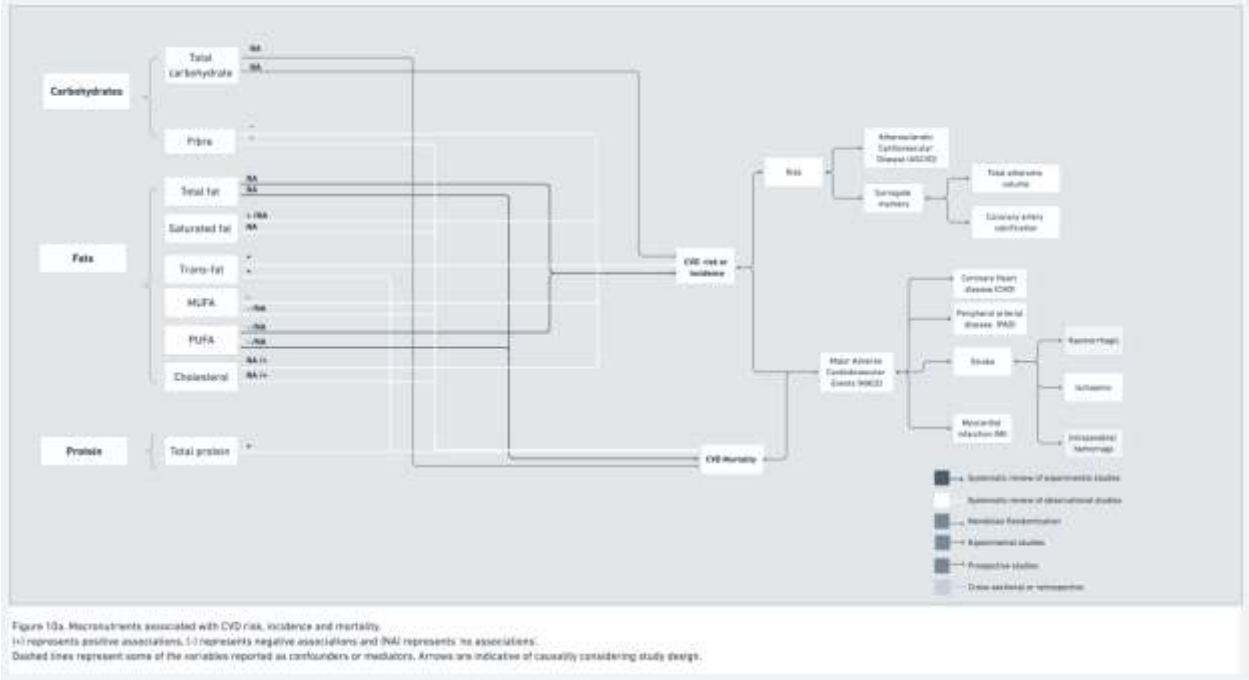

Figure 10a. Macronutrients associated with CVD risk, incidence and mortality.
(+) represents positive associations, (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

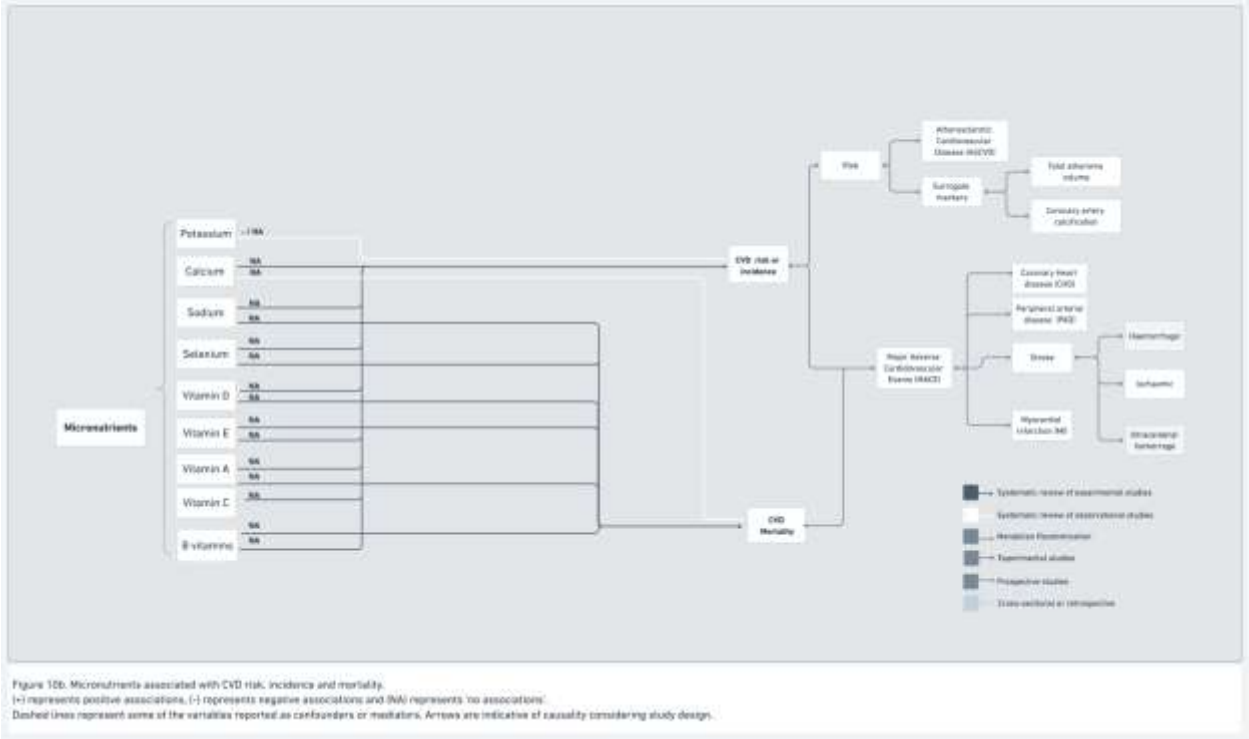

Figure 10b. Micronutrients associated with CVD risk, incidence and mortality.

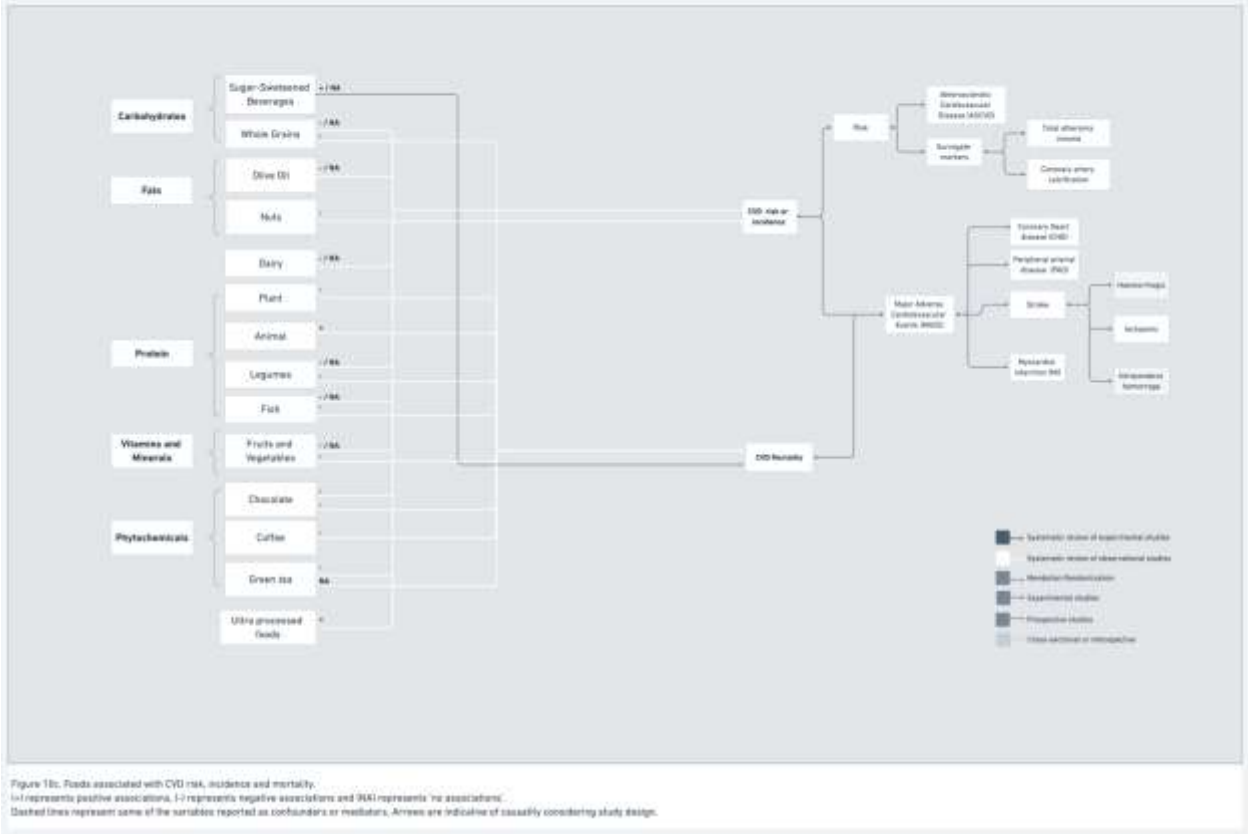

Figure 10c. Foods associated with CVD risk, incidence and mortality.

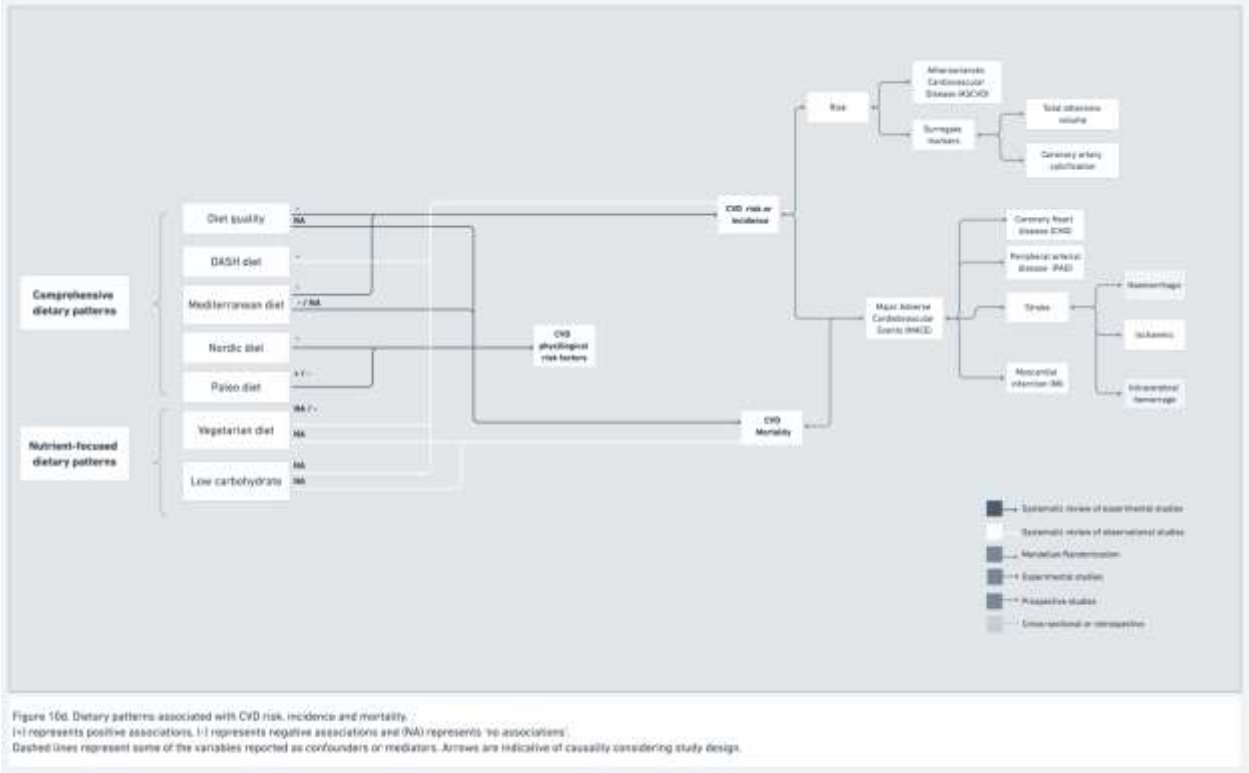

Figure 10d. Dietary patterns associated with CVD risk, incidence and mortality.
(+) represents positive associations, (-) represents negative associations and (NA) represents 'no associations'.
Dashed lines represent some of the variables reported as confounders or mediators. Arrows are indicative of causality considering study design.

Figure 10d.Dietary patterns associated with CVD risk, incidence and mortality.